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(54) Title: IMMUNOSUPPRESSIVE AND TOLEROGENIC MODIFIED LEWISc AND LacNAc COMPOUNDS

(57) Abstract

Disclosed are novel Lewisc and LacNAc analogues, pharmaceutical compositions containing such analogues, methods for their preparation and methods for their use.

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IMMUNOSUPPRESSIVE AND TOLEROGENIC
MODIFIED LEWIS[c] AND LacNAc COMPOUNDS

BACKGROUND OF THE INVENTION

1.   Field of the Invention.

5   The present invention is directed to
Lewis[c]-YR and LacNAc-YR analogues, pharmaceutical
compositions containing such analogues, methods for
their preparation and methods for their use.

2.   References

10   The following references are cited in this
application as superscript numbers at the relevant
portion of the application:

     1   Horowitz, "The Glycoconjugates", Vols. I-V,
         Pigman, Editor, New York Academic Press
15   (1977, 1978, 1982, 1983).

     2   Ippolito, et al., U.S. Patent Application
         Serial No. 07/714,161, filed June 10, 1991
         for "Immunosuppresive and Tolerogenic
         Oligosaccharide Glycosides".

20   3   Sialic Acids in "Cell Biology Monographs"
         Schauer, Editor, Vol. 10 (1982).

     4   Lowe, et al., Cell, 63:475-485 (1990).

     5   Phillips, et al., Science, 250:1130-1132
         (1990).

25   6   Walz, et al., Science, 250:1132 et seq.
         (1990).

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7   Larsen, et al., Cell, <u>63</u>:467-474 (1990).

8   Ratcliffe, et al., U.S. Patent No. 5,079,353, issued January 7, 1992, for "Sialic Acid Glycosides, Antigens, Immunoadsorbents, and Methods for their Preparation".

9   Ratcliffe, et al., U.S. Patent Application Serial No. 07/278,106, filed November 30, 1988, for "Sialic Acid Glycosides, Antigens, Immunoadsorbents, and Methods for their Preparation".

10   Venot, et al., U.S. Patent Application Serial No. 07/771,007, "Methods for the Enzymatic Synthesis of Alpha-sialylated Oligosaccharide Glycosides", filed October 2, 1991.

11   Weinstein, et al., J. Biol. Chem., <u>257</u>:13845-13853 (1982).

12   Reuter, et al., Glycoconjugate J., <u>5</u>:133-135 (1988).

13   Ippolito, et al., U.S. Patent Application Serial No. 07/889,017, filed May 26, 1992 for "Immunosuppresive and Tolerogenic Oligosaccharide Glycosides".

14   Smith, et al., Immunology, <u>58</u>:245 (1986).

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16   Hindsgaul, et al., Carbohydr. Res., <u>109</u>:109-142 (1982).

17   Nicolaou, et al., J. Amer. Chem. Soc., <u>112</u>:3693-3695 (1990).

18   Ekborg, et al., Carbohydr. Res., <u>110</u>:55-67 (1982).

19   Dahmen, et al., Carbohydr. Res., <u>118</u>:292-301 (1983).

20   Rana, et al., Carbohydr. Res., <u>91</u>:149-157 (1981).

21   Amvam-Zollo, et al., Carbohydr. Res., <u>150</u>:199-212 (1986).

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22   Paulsen, et al., Carbohydr. Res., 104:195-219 (1982).

23   Chernyak, et al., Carbohydr. Res., 128:269-282 (1984).

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25   Lee et al., Carbohydr. Res., 37:193 et seq. (1974).

26   Norberg, et al., Carbohydr. Res., 183:71 et seq. (1988).

27   Petitou, et al., Carbohydr. Res., 147:221-236 (1986).

28   Trumtez, et al., Carbohydr. Res., 191:29-52 (1989).

29   Lemieux, et al., J. Amer. Chem. Soc., 97:4076-4083 (1975).

30   Lemieux, et al., Can. J. Chem. 60:63-67 (1982).

31   Okamoto, et al., Tetrahedron, Vol. 46, No. 17, pp. 5835-5837 (1990).

32   Abbas, et al., Proc. Japanese-German Symp. Berlin, pp. 20-21 (1988).

33   Paulsen, Agnew. Chem. Int. Ed. Eng., 21:155-173 (1982).

34   Schmidt, Agnew. Chem. Int. Ed. Eng., 25:212-235 (1986).

35   Fügedi, et al., Glycoconj. J., 4:97-108 (1987).

36   Kameyama, et al., Carbohydr. Res., $209:C_1-C_4$ (1991).

37   Inazu, et al., Bull. Soc. Chim., Jap., 611:4467 (1988).

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39   Wollenberg, et al., U.S. Patent No.
      4,612,132, for Issued September 21, 1986 for
      "Modified Succinimides".

40   Greig, et al., J. Chem. Soc., p. 879 (1961).

41   Piekarska-Bartowzewicz, et al., Carbohydr.
      Res., 203:302-307 (1990).

All publications and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

3.   State of the Art

Carbohydrates and/or oligosaccharides are present on a variety of natural and pathological glycoconjugates[1]. Of particular interest are carbohydrates and oligosaccharides containing sialyl and/or fucosyl residues[3]. Such sialyl and/or fucosyl carbohydrates and oligosaccharides are present in a number of products which have been implicated in a wide range of biological phenomena based, in part, on the concept of recognition signals carried by the carbohydrate structures and by their binding to specific ligands.

Specifically, a number of sialylated and sialylated/fucosylated oligosaccharide glycosides have been proposed as mediators of cell adhesion in that they are ligands for selectins (or LEC-CAM's)[4,5,6,7]. Sialylated, fucosylated, and sialylated and fucosylated oligosaccharide structures relating to blood group

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determinants having a type I or a type II core
structure, including Lewis[X], Lewis[A], sialyl Lewis[X] and
sialyl Lewis[A], have also been shown by Ippolito et
al.[2,13] to possess $\underline{in}$ $\underline{vivo}$ immunomodulating and
5   tolerogenic properties in mammals including anti-
inflammatory immunomodulating properties.

In regard to the above, the DTH anti-
inflammatory immunomodulating properties of Lewis[X] and
sialyl Lewis[X] reported by Ippolito et al.[2,13]
10   demonstrate that the presence of the sialyl residue on
sialyl Lewis[X] results in enhanced anti-inflammatory
activity as compared to Lewis[X] and that the presence of
a fucosyl group on sialyl Lewis[X] results in enhanced
anti-inflammatory activity as compared the anti-
15   inflammatory activity of sialyl LacNAc.

Contrarily, oligosaccharide glycosides
containing a sialyl group and/or a fucosyl group as
well as related compounds are difficult to chemically
synthesize in high yield. For example, synthesis of
20   the αNeu5Ac(2$\rightarrow$3)βGal disaccharide unit in compounds
such as sialyl Lewis[X] and sialyl Lewis[A] with anomeric
specificity for the α(2$\rightarrow$3) is known to be difficult.
Known chemical methodologies include a multistep
synthesis which first generates a blocked
25   αNeu5Ac(2$\rightarrow$3)Gal disaccharide having a suitable leaving
group at the reducing sugar terminus of the
galactose[8,9]. This disaccharide is then reacted with a
suitably protected GlcNAc-OR saccharide glycoside and
then a suitably protected L-fucose derivative which,
30   after deprotection, provides for the sialyl Lewis[X]
glycoside [αNeu5Ac(2$\rightarrow$3)βGal(1$\rightarrow$4)[αFuc(1$\rightarrow$3)]-βGlcNAc-OR]
or the sialyl Lewis[A] glycoside [i.e,

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αNeu5Ac(2$\rightarrow$3)βGal(1$\rightarrow$3)-[αFuc(1$\rightarrow$4)]-βGlcNAc-OR] where R
is an aglycon of at least one carbon atom.

     While it is well known that sialylation and
fucosylation can be conducted as part of an overall
chemical/enzymatic synthesis[2,9,10] of compounds such as
sialyl Lewis[A] and sialyl Lewis[X], such processes require
compatible sialyltransferases and fucosyltransferases
which are not always readily available. For example,
the βGal(1$\rightarrow$3/4)βGlcNAc α(2$\rightarrow$3)sialyltransferase
disclosed in the art for sialylating the
βGal(1$\rightarrow$4)βGlcNAc backbone is currently recovered from
rat livers[11].

     In any event, the inclusion of a sialyl
and/or a fucosyl residue on LacNAc-OR and Lewis[c]-OR so
as to provide for sialyl and/or fucosylated derivatives
results in a more complex and costly synthesis.

SUMMARY OF THE INVENTION
     The present invention is directed, in part,
to the discovery that modified Lewis[c]-YR and modified
LacNAc-YR compounds having a sulfate, a phosphate or a
carboxylate containing group at the 2, 3 and/or 6-
positions of the galactose unit possess good
immunosuppressive and tolerogenic properties.
Moreover, the 3-sulfate Lewis[c]-YR compound possesses
approximately equivalent immunosuppressive properties
as compared to sialyl Lewis[X]-YR. This result is
particularly surprising insofar as unmodified Lewis[A]-YR
and sialyl Lewis[A]-YR possess inferior immunosuppressive
properties as compared to the 3-sulfate of Lewis[c]-YR.
Additionally, these modified LacNAc-YR and modified
Lewis[c]-YR compounds do not require formation of an

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α(2→3) sialyl residue on the galactose or a fucosyl
residue at the 3- or 4-position of the GlcNAc residue
in order to impart biological activity. Accordingly,
the synthesis of biologically active molecules is

5   simplified and the inclusion of a required sialyl group
or a required fucosyl group is avoided. However, in
this regard, the optional inclusion of a sialyl group
at the 6-position of the galactose having a sulfate,
phosphate or $-CHR_{18}COOH$ group at the 2- or 3-position of

10   the galactose is contemplated herein.

        Accordingly, in one of its composition
aspects, the present invention is directed to compounds
of Formula I or II:
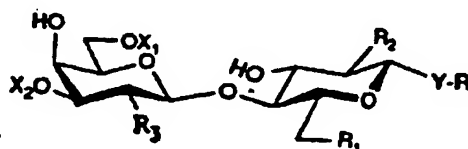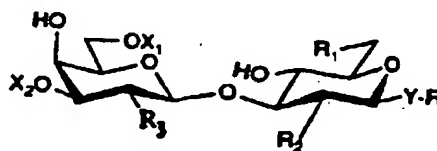
        where R is selected from the group consisting of
hydrogen, a saccharide-OR_{19}, an oligosaccharide-OR_{19}
having from 2 to 7 oligosaccharide units, or an aglycon
having at least 1 carbon atom where R_{19} is hydrogen or

20   an aglycon of at least one carbon atom;
        Y is selected from the group consisting of oxygen,
sulfur, and -NH-;
        R_1 is selected from the group consisting of
hydrogen, $-NH_2$, $-N_3$, $-NHSO_3H$, $-NR_5C(O)R_4$, $-N=C(R_5)_2$,

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$-NHCH(R_5)_2$, $-NHR_6$, $-N(R_6)_2$, $-OH$, $-OR_6$, $-S(O)R_6$, $-S(O)_2R_6$ and sulfate,

wherein R_4 is selected from the group consisting of

5   hydrogen,

alkyl of from 1 to 4 carbon atoms;

$-OR_7$ wherein R_7 is alkyl of from 1 to 4 carbon atoms, or alkyl of from 2 to 4 carbon atoms substituted with a hydroxyl group, and

10           $-NR_8R_9$ wherein R_8 and R_9 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 4 carbon atoms,

each R_5 is selected from the group consisting of hydrogen and alkyl of from 1 to 4 carbon atoms,

15   each R_6 is alkyl of from 1 to 4 carbon atoms,

R_2 is selected from the group consisting of hydrogen, $-N_3$, $-NH_2$, $-NHSO_3H$, $-NR_{11}C(O)R_{10}$, $-N=C(R_{11})_2$, $-NHCH(R_{11})_2$, $-NHR_{12}$, $-N(R_{12})_2$, $-OH$ and $-OR_{12}$,

wherein R_{10} is selected from the group consisting

20   of

hydrogen,

alkyl of from 1 to 4 carbon atoms,

$-OR_{13}$ wherein R_{13} is alkyl of from 1 to 4 carbon atoms, or alkyl of from 2 to 4 carbon atoms

25   substituted with a hydroxyl group, and

$-NR_{14}R_{15}$ wherein R_{14} and R_{15} are independently selected from the group consisting of hydrogen and alkyl of from 1 to 4 carbon atoms,

each R_{11} is selected from the group consisting of

30   hydrogen and alkyl of from 1 to 4 carbon atoms;

each R_{12} is alkyl of from 1 to 4 carbon atoms,

R_3 is selected from the group consisting of hydrogen, fluoro, sulfate and hydroxy;

X_1 is selected from the group consisting of

35   hydrogen, sialyl, sulfate, phosphate, and $-CHR_{18}COOH$

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where R_{18} is selected from the group consisting of.
hydrogen, alkyl of from 1 to 7 carbon atoms and
-COOH;

     X_2 is selected from the group consisting of
hydrogen, sulfate, phosphate, and $-CHR_{18}COOH$ where R_{18}
is selected from the group consisting of hydrogen,
alkyl of from 1 to 7 carbon atoms and -COOH; and
     pharmaceutically acceptable salts thereof;
     and with the proviso that either at least one of
X_1 or X_2 is sulfate, phosphate or $-CHR_{18}COOH$ or R_3 is
sulfate.

     The compounds of Formula I and II are useful
in modulating a cell-mediated immune inflammatory
response and in particular a cell-mediated immune
inflammatory response to an antigen.

     The compounds of this invention are
particularly useful in reducing antigen induced
inflammation in a sensitized mammal. In this regard,
when the compounds of. Formula I and II are administered
to a sensitized mammal in response to an antigen
challenge, such administration induces tolerance to
later challenges from this same antigen. Preferably,
administration of a compound of Formula I or II above
is after initiation of the mammal's immune response but
at or prior to one-half of the period of time required
for the mammal to reach maximal inflammation.

     In another of its composition aspects, the
present invention is directed to a pharmaceutical
composition suitable for administration to a mammal
(e.g., human) which comprises a pharmaceutically inert
carrier and an effective amount of the compound of

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Formula I or Formula II to modulate a cell-mediated
immune inflammatory responses in said mammal.

In one of its method aspects, the present
invention is directed to a method for modulating a
5   cell-mediated immune inflammatory response in a mammal
which method comprises administering to said mammal an
amount of a compound of Formula I or Formula II
effective in modulating said immune response.

BRIEF DESCRIPTION OF THE DRAWINGS
10   Figure 1 illustrates reaction schemes for the
synthesis of partially blocked N-acetyl glucosamine
derivatives which are then used to prepare either
modified Lewis^c-OR compounds or modified LacNAc
compounds.

15   Figure 2 illustrates reaction schemes for the
synthesis of partially blocked galactose derivatives
which are then used to prepare either modified Lewis^c-
OR compounds or modified LacNAc-OR compounds.

Figure 3A illustrates one method for the
20   preparation of 3-sulfated Lewis^c-OR compounds.

Figure 3B illustrates one method for the
preparation of 6-sulfated Lewis^c-OR compounds.

Figure 4 illustrates methods for preparing
differentially blocked βGal(1→3)βGlcNAc-OR compounds
25   (Lewis^c-OR) and derivatives thereof and methods for
preparing differentially blocked βGal(1→4)βGlcNAc-OR
(LacNAc-OR) compounds.

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Figure 5 illustrates the synthesis of the
6-azido derivative of GlcNAc-OR.

Figure 6 illustrates the synthesis of the 6-
alkoxy derivatives and the 6-deoxy derivatives of
5   GlcNAc-OR.

Figure 7 illustrates the preparation of 3-
hydroxy or 4-hydroxy blocked GlcNH$_2$-OR where the amino
group is protected as an N-phthalimido group.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS
10   As noted above, the present invention is
directed, in part, to the discovery of novel Lewis^c-YR
and novel LacNAc-YR analogues which, in mammals,
including humans, are useful for in vivo modulation
(e.g., suppression) of a cell mediated immune response
15   including cell-mediated and immune directed
inflammatory responses to an antigen in a sensitized
mammal (e.g., a DTH response).

However, prior to discussing this invention
in further detail, the following terms will first be
20   defined.

Definitions
             As used herein, the following terms have the
definitions given below:

The term "cell-mediated immune response in a
25   mammal" refers to those mammalian immune responses
which are mediated by cell-cell interactions. Included
within this term are cell mediated inflammatory
responses to an antigen such as DTH responses as well

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as cell-mediated inflammatory responses arising from
injury such as frost-bite injury, reperfusion injury,
adult respiratory distress syndrome, and the like.
Preferably, the cell-mediated immune response is a
5   leucocyte-mediated response.

The term "antigen" refers to any protein,
peptide, carbohydrate, nucleic acid or other non-
endogenous substance which when exposed to a mammal
induces an immune response in that mammal.

10   Disease conditions believed to be caused by
antigen exposure include, by way of example, psoriasis,
asthma, dermatitis, rheumatoid arthritis, delayed type
hypersensitivity, inflammatory bowel disease, multiple
scelorsis, viral pneumonia, bacterial pneumonia, and
15   the like.

The term "sensitized mammal" refers to those
mammals which have been previously exposed to an
antigen and, accordingly, their immune systems have
become educated to that antigen. Typically, initial
20   exposure of an antigen to a mammal primes or educates
the mammal's immune response to later exposure to that
antigen with minimal inflammation during such initial
exposure.

The term "secondary immune response" refers
25   to the effector phase of a mammal's immune response to
an antigen to which it has been previously been
sensitized. A mammal's secondary immune response is
typically accompanied by inflammation at the point of
antigen exposure.

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The term "period for maximal inflammation"
refers to the period of time typically required to
achieve maximal inflammation in a sensitized mammal due
to exposure to a specific antigen or to the period of
5   time typically required to achieve maximal inflammation
in a mammal due to an injury which induces a cell-
mediated inflammatory response (e.g., myocardial
infarction). This period of time depends on several
factors. For example, for inflammation due to injury,
10   the period for maximal inflammation depends on factors
such as the type and extent of injury. In a sensitized
mammal exposed to an antigen, this period is dependent
on factors such as the specific antigen to which the
mammal has been exposed, the particular mammalian
15   species exposed to the antigen, etc. Accordingly, the
period of time required to effect maximal antigen
induced inflammation in·a sensitized mammal will vary
for, by way of example, asthma as opposed to rheumatoid
arthritis.

20   Moreover, while the specific time required to
effect maximal inflammation will vary somewhat in a
given mammalian species, the time typically required to
effect maximal inflammation for different antigen
exposures in human and other mammals resulting in
25   asthma, rheumatoid arthritis, psorasis, DTH, etc. is
known in the art or are readily ascertainable by the
skilled artisan. For example, in the case of a DTH
response in mice, maximal inflammation is typically 24
hours after antigen exposure.

30   The term "LacNAc" refers to the disaccharide
$\beta Gal(1\rightarrow4)\beta GlcNAc$. Because of its relationship to the
core structure of type II blood group determinants, the

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βGal(1→4)βGlcNAc structure of LacNAc is often referred
to as a type II structure.

The term "LacNH₂" refers to the LacNAc
derivative wherein the N-acetyl group of LacNAc has
5   been replaced with an amine (-NH₂).

The term "LacN₃" refers to the LacNAc
derivative wherein the N-acetyl group of LacNAc has
been replaced with an azido (-N₃).

The term "Lewis^c" (sometimes referred to
10   "Le^c") refers to the disaccharide βGal(1→3)βGlcNAc.
Because of its relationship to the core structure of
type I blood group determinants, the βGal(1→3)βGlcNAc
structure of Lewis^c is often referred as a "type I
structure".

15   The terms "modified Lewis^c glycosides
(Lewis^c-YR) and derivatives thereof" refer to
derivatives of the Lewis^c modified in one or both of
the galactose and N-acetylglucosamine saccharide units
of Lewis^c and which have an -YR substituent as defined
20   above. When the R substituent is an aglycon group,
this group has at least one carbon atom, but
nevertheless is different from glycoconjugates because
such aglycon moieties are neither a protein nor a lipid
capable of forming a micelle or other large aggregate
25   structure.

The term "modified LacNAc glycosides
(LacNAc-YR) and derivatives thereof" refer to
derivatives of the LacNAc modified in one or both of
the galactose and N-acetylglucosamine saccharide units
30   of LacNAc and which have an -YR substituent as defined

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above. When the R substituent is an aglycon group,
this group has at least one carbon atom, but
nevertheless is different from glycoconjugates because
such aglycon moieties are neither a protein nor a lipid
5   capable of forming a micelle or other large aggregate
structure.

The term "aglycon of at least one carbon
atom" refers to non-saccharide containing residues
having at least one carbon atom. Preferably, the
10   aglycon moiety, R, is selected from the group
consisting of -(A)-Z wherein A represents a bond, an
alkylene group of from 2 to 10 carbon atoms, and a
moiety of the formula $-(CH_2-CR_{20}G)_n-$ wherein n is an
integer equal to 1 to 5; R_{20} is selected from the group
15   consisting of hydrogen, methyl, or ethyl; and G is
selected from the group·consisting of hydrogen,
halogen, oxygen, sulphur, nitrogen, phenyl and phenyl
substituted with 1 to 3 substituents selected from the
group consisting of amine, hydroxyl, halo, alkyl of
20   from 1 to 4 carbon atoms and alkoxy of from 1 to 4
carbon atoms; and Z is selected from the group
consisting of hydrogen, methyl, phenyl, nitrophenyl,
aminophenyl and, when G is not oxygen, sulphur or
nitrogen and A is not a bond, then Z is also selected
25   from the group consisting of $-OH$, $-SH$, $-NH_2$, $-NHR_{21}$,
$-N(R_{21})_2$, $-C(O)OH$, $-C(O)OR_{21}$, $-C(O)NH-NH_2$, $-C(O)NH_2$,
$-C(O)NHR_{21}$, $-C(O)N(R_{21})_2$, and $-OR_{22}$ wherein each R_{21} is
independently alkyl of from 1 to 4 carbon atoms and R_{22}
is an alkenyl group of from 3 to 10 carbon atoms.

30   Numerous aglycons are known in the art. For
example, an aglycon comprising a para-nitrophenyl group
(i.e., $-YR = -OC_6H_4pNO_2$) has been disclosed by Ekborg,
et al.[18]   At the appropriate time during synthesis, the

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nitro group is reduced to an amino group which can be protected as N-trifluoroacetamido. The trifluoro-acetamido group can later be removed thereby unmasking the amino group which can then be used to further
5   functionalize the aglycon group.

An aglycon containing sulfur is disclosed by Dahmen, et al.[19]. Specifically, the aglycon is derived from a 2-bromoethyl group which, in a substitution reaction with thionucleophiles, has been shown to lead
10   to aglycons possessing a variety of terminal functional groups such as $-OCH_2CH_2SCH_2CO_2CH_3$ and $-OCH_2CH_2SC_6H_4-pNH_2$.

Rana, et al.[20] discloses a 6-trifluoroacet-amidohexyl aglycon $(-O-(CH_2)_6-NHCOCF_3)$ in which the trifluoroacetamido protecting group can be removed
15   unmasking the primary amino group which can then be used to further functionalize the aglycon group.

Other exemplification of known aglycons include the 7-methoxycarbonyl-3,6,dioxaheptyl aglycon[21] $(-OCH_2-CH_2)_2OCH_2CO_2CH_3$; the 2-(4-methoxycarbonylbutane-
20   carboxamido)ethyl[22] $(-OCH_2CH_2NHC(O)(CH_2)_4CO_2CH_3)$; and the allyl aglycon[23] $(OCH_2CH=CH_2)$ which, by radical co-polymerization with an appropriate monomer, leads to co-polymers; other allyl aglycons[24] are known [e.g., $-O(CH_2CH_2O)_2CH_2CH=CH_2$]. Additionally, allyl aglycons
25   can be derivatized in the presence of 2-aminoethane-thiol[25] to provide for aglycons $-OCH_2CH_2CH_2SCH_2CH_2NH_2$. Still other aglycons are illustrated hereinbelow.

Additionally, as shown by Ratcliffe et al.[9], the R group can be an additional saccharide-OR_{19} or an
30   oligosaccharide-OR_{19} containing an aglycon at the reducing sugar terminus.

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Preferably, the aglycon moiety is a hydrophobic group and most preferably, the aglycon moiety is a hydrophobic group selected from the group consisting of $-(CH_2)_8COOCH_3$, $-(CH_2)_5OCH_2CH=CH_2$ and

5      $-(CH_2)_8CH_2OH$.

The term "oligosaccharide" refers to a carbohydrate structure having from 2 to about 7 saccharide units. The particular saccharide units employed are not critical and include, by way of

10   example, all natural and synthetic derivatives of glucose, galactose, N-acetylglucosamine, N-acetyl-galactosamine, fucose, sialic acid, 3-deoxy-D,L-octulosonic acid, and the like. In addition to being in their pyranose form, all saccharide units described

15   herein are in their D form except for fucose which is in its L form.

The term "sialic acid" or "sialyl" means all naturally occurring structures of sialic acid and analogues of sialic acid. Naturally occurring

20   structures of sialic acid include, by way of example, 5-acetamido-3,5-dideoxy-D-glycero-D-galactononulo-pyranosylonic acid ("Neu5Ac"), N-glycoyl neuraminic acid (Neu5Gc) and 9-O-acetyl neuraminic acid (Neu5,9Ac$_2$). Analogues of sialic acid refers to

25   analogues of naturally occurring structures of sialic acid including those wherein the sialic acid unit has been chemically modified so as to introduce and/or remove one or more functionalities from such structures. For example, such modification can result

30   in the removal of an -OH functionality, the introduction of an amine functionality, the introduction of a halo functionality, and the like.

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Certain analogues of sialic acid are known in the art and include, by way of example, 9-azido-Neu5Ac, 9-amino-Neu5Ac, 9-deoxy-Neu5Ac, 9-fluoro-Neu5Ac, 9-bromo-Neu5Ac, 7-deoxy-Neu5Ac, 7-epi-Neu5Ac, 7,8-bis-epi-Neu5Ac, 4-O-methyl-Neu5Ac, 4-N-acetyl-Neu5Ac, 4,7-di-deoxy-Neu5Ac, 4-oxo-Neu5Ac, as well as the 6-thio analogues of Neu5Ac. The nomenclature employed herein in describing analogues of sialic acid is as set forth by Reuter et al.[12]

The term "pharmaceutically acceptable salts" includes the pharmaceutically acceptable addition salts of the compounds of Formula I or Formula II derived from a variety of organic and inorganic counter salts well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like.

The term "sulfate" such as used to define the substituents $-X_1$ and $-X_2$ refers to substituents which, with the oxygen of a hydroxyl group of the galactose unit, form a sulfate group (i.e., $-O-S(O)_2-OH$). Thus, when X_1 or X_2 is a sulfate, the resulting $-OX_1$ and/or $-OX_2$ group is $-O-S(O)_2-OH$, which readily forms pharmaceutically acceptable salts thereof (e.g., $-O-S(O)_2-O^-Na^+$). Contrarily, the term "sulfate" as it is used for R_3 refers to the $-O-S(O_2)-OH$ group, which readily forms pharmaceutically acceptable salts thereof.

The term "phosphate" such as used to define the substituents $-X_1$ and $-X_2$ refers to substituents which, with the oxygen of a hydroxyl group of the galactose unit, form a phosphate group (i.e.,

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$-O-P(O)-(OH)_2$. Thus, when X_1 or X_2 is a phosphate, the resulting $-OX_1$ and/or $-OX_2$ group is $-O-P(O)-(OH)_2$, which readily forms pharmaceutically acceptable salts thereof (e.g., $-O-P(O)-(O^-Na^+)_2$.

5   The term "removable blocking group" or "blocking group" refers to any group which when bound to one or more hydroxyl groups of the galactose and/or the N-acetylglucosamine of the Lewis^c-YR and LacNAc-YR compounds prevents reactions from occurring at these
10   hydroxyl groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the hydroxyl group. The particular removable blocking group employed is not critical and preferred removable hydroxyl blocking groups include
15   conventional substituents such as benzyl, benzoyl, acetyl, chloroacetyl, benzylidine, t-butyldiphenyl-silyl and any other group that can be introduced either enzymatically or chemically onto a hydroxyl functionality and later selectively removed either by
20   enzymatic or chemical methods in mild conditions compatible with the nature of the product. One such contemplated blocking group is a α-galactose which can be removed enzymatically with an α-galactosidase.

2.   Methodology
25   The modified Lewis^c-YR and modified LacNAc-YR compounds disclosed herein are readily prepared by complete chemical syntheses.

The figures attached hereto elaborate on a variety of complete chemical synthetic schemes which
30   result in the preparation of modified Lewis^c-YR and modified LacNAc-YR compounds.

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Chemical synthesis is a convenient method for preparing either the complete oligosaccharide glycoside; for chemically modifying a saccharide unit which can then be chemically or enzymatically coupled to an oligosaccharide glycoside; or for chemically preparing an oligosaccharide glycoside to which can be enzymatically coupled one or more saccharide units.

Several chemical syntheses of blocked intermediates exist[16,17,30] and, with suitable modifications to these synthetic routes, can be used herein. Syntheses of these intermediates or similar ones utilizing methods known in the art allow the synthesis of the modified Lewis[c]-YR and modified LacNAc-YR compounds disclosed herein.

Chemical modifications include introduction of the sulphate or phosphate group or a $-OCHR_{18}COOH$ at the 3 and/or 6 position of the terminal galactose; the introduction of a sulfate at the 2-position of the galactose; and optionally, the introduction of modification at the 2- and 6- positions of the N-acetylglucosamine unit and/or introduction of deoxy or fluoro functionality at the 2-position of the galactose, and the like.

In the description below as well as in the examples and figures, reference is made to the -OR group at the reducing sugar. However, it is understood that this group could also be -NHR or -SR, the preparation of which is well known in the art.

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2A. CHEMICAL SYNTHESIS OF SACCHARIDE MONOMERS

Chemical methods for the synthesis of Lewis^c-YR and LacNAc-YR and some analogues thereof are known in the art. These materials are generally
5   assembled using suitably protected individual monosaccharide intermediates. The modifications to the final structures are accomplished using known methods for sulfation or phosphorylation after appropriate selective deblocking of the to-be functionalized
10   hydroxyl group(s) of the fully blocked Lewis^c-YR or LacNAc-YR.

The specific methods employed are generally adapted and optimized for each individual structure to
15   be synthesized. In general, the chemical synthesis of all or part of the these disaccharides first involves formation of a glycosidic linkage on the anomeric carbon atom of the reducing sugar. Specifically, an appropriately protected form of a naturally occurring
20   or of a chemically modified saccharide structure (the glycosyl donor) is selectively modified at the anomeric center of the reducing unit so as to introduce a leaving group comprising halides, trichloroacetimidate, acetyl, thioglycoside, etc. The donor is then reacted
25   under catalytic conditions well known in the art with an aglycon or an appropriate form of a carbohydrate acceptor which possess one free hydroxyl group at the position where the glycosidic linkage is to be established. A large variety of aglycon moieties are
30   known in the art and can be attached with the proper configuration to the anomeric center of the reducing unit. Appropriate use of compatible blocking groups, well known in the art of carbohydrate synthesis, will allow selective modification of the synthesized

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structures or the further attachment of additional
sugar units or sugar blocks to the acceptor structures.

5   After formation of the glycosidic linkage,
the saccharide glycoside can be used to effect coupling
of the galactose unit or chemically modified at
selected positions. In general, chemical coupling of a
naturally occurring or chemically modified saccharide
unit to the saccharide glycoside is accomplished by
employing established chemistry well documented in the
10 literature. See, for example, Okamoto et al.[31],
Ratcliffe et al.[8], Abbas et al.[32], Paulsen[33], Schmidt[34],
Fugedi et al.[35], and Kameyama et al.[36]

With reference to the figures, Figure 1
illustrates the synthesis of numerous blocked
15 derivatives of glucosamine and N-acetylglucosamine
which are then useful in the preparation of blocked
LacNH$_2$-OR [βGal(1→4)βGlcNH$_2$-OR], LacNAc-OR
[βGal(1→4)βGlcNAc-OR], Lewis^c-OR [βGal(1→3)βGlcNAc-OR],
Lewis^c-NH$_2$-OR [βGal(1→3)βGlcNH$_2$-OR], etc. structures.
20 Specifically, in Figure 1, glucosamine hydrochloride is
slurried in dichloroethane containing an equivalent of
anhydrous sodium acetate to which acetic anhydride is
added dropwise and, after addition is completed, the
solution is refluxed for a period of from about 12-16
25 hours to provide for the peracylated compound 10 (about
3:1 ratio of α/β).

Alternatively, the glucosamine hydrochloride
is first taken up in methanol and then treated with 1
equivalent of metallic sodium to neutralize the HCl.
30 Phthalic anhydride is then added quickly to the
reaction mixture followed shortly thereafter by
triethylamine to provide for the phthalimido

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derivative. This compound is then isolated and
acetylated with acetic anhydride/pyridine using
conventional techniques to provide for peracylated
compound 1 having a phthalimide blocking group
5   protecting the amine.

Afterwards, the aglycon is formed by
conventional techniques. For example, compound 10 is
converted to 1-α-chloro compound 2 by well known
chemistry which involves bubbling saturating amounts of
10   hydrogen chloride directly into a dichloroethane
solution of compound 10. In this regard, the solution
used to prepare compound 10 can be used in this
reaction after that solution has been quenched into
water to remove acetic anhydride and sodium acetate,
15   dried and recovered. The reaction generally proceeds
over a period of about 4-6 days and hydrogen chloride
is bubbled into the solution periodically (e.g., about
once ever 1-2 days). After reaction completion, the
solution is quenched in aqueous sodium bicarbonate at
20   about 0-5°C and the product is recovered after drying
the organic layer and stripping the solution to provide
for compound 2 (one spot on t.l.c.)

Compound 2 is then converted to the
1-β-(CH$_2$)$_8$COOCH$_3$ aglycon by well known chemistry which
25   involves reaction of compound 2 with HO(CH$_2$)$_8$COOCH$_3$ in
anhydrous dichloromethane containing molecular sieves
in the presence of an equivalent amount of mercuric
cyanide. The reaction is generally conducted at room
temperature for a period of about 12 to 24 hours. Upon
30   reaction completion (as evidenced by t.l.c.), the
reaction solution is filter through silica and the
resulting solution is quenched by adding the reaction
solution to cold water. The organic layer is recovered

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and the washed twice with an aqueous potassium iodide
(5 weight/vol percent) solution and then with a
saturated aqueous sodium bicarbonate solution. The
resulting organic solution is then dried and the
5   solvent removed by stripping to provide for
compound 3.

The 3, 4, and 6 hydroxyl groups of compound 3
are then deprotected by reaction with sodium methoxide
in methanol to provide for N-acetylglucosamine-OR,
10   compound 4. This compound can reacted with
$C_6H_5CH(OCH_3)_2$ in, for example, an acidic medium in an
appropriate solvent at around 40-50°C for about 4-6
hours to provide for the 4,6-O-diprotected benzylidine
compound 5. In turn, compound 5 can be reacted with p-
15   methoxybenzyl trichloroacetimidate in an appropriate
solvent (e.g., DMF, dichloromethane) in the presence of
a catalytic amount of an acid (e.g., p-toluenesulfonic
acid -- pTSA) to provide for the p-methoxybenzyl
protected 3-hydroxy compound 6. Treatment of compound
20   6 with sodium cyanoborohydride in tetrahydrofuran
followed by the dropwise addition of HCl saturated
ether at about 0°C leads to compound 7.

Alternatively, compound 5 can be blocked at
the 3-hydroxyl group by reaction with, for example,
25   allyl bromide and base (e.g., barium hydroxide/barium
oxide) to provide for compound 8. Treatment of
compound 8 with sodium cyanoborohydride in tetrahydro-
furan followed by the dropwise addition of HCl
saturated ether at about 0°C leads to compound 9.

30   Because compounds 7 and 9 contain only a
free hydroxyl group at the 4-position of the blocked
GlcNAc-OR saccharide, subsequent reaction with an

-- 25 --

appropriately blocked galactose will result in
formation of a blocked type II LacNAc-OR structure
[βGal(1→4)βGlcNAc-OR].

Because compound **5** contains a free hydroxyl
group only at the 3-position of the blocked GlcNAc-OR
saccharide, subsequent reaction with an appropriately
blocked galactose will result in formation of a blocked
type I structure [βGal(1→3)βGlcNAc-OR].

Alternatively, compound **1** can be converted to
compound **11** by reaction of compound **1** with an
equivalent of p-chlorothiophenol in dichloromethane at
room temperature in the presence of 2 equivalents of
boron trifluoride etherate (BF$_3$·etherate) to provide for
compound **11**.

In yet another embodiment, compound **1** is
converted to compound **12** (or the bromo analogue) by
following similar procedures set forth above for
compound **2**.

Compound **12** is converted to compound **13** by
reaction with an alcohol (e.g., ethanol, R = -CH$_2$CH$_3$) in
manner similar to that of compound **3** with the exception
that the alcohol replaces HO(CH$_2$)$_8$COOCH$_3$. Compound **13**
is then converted to compound **14** with sodium
methoxide/methanol and is then converted to compound **15**
by reaction with bis[tributyltin] oxide in refluxing
toluene containing tetraethylammonium bromide followed
by reaction with benzyl bromide.

Because compound **15** contains free hydroxyl
groups at the 3- and 4-positions of the blocked GlcNAc-
OR saccharide, subsequent reaction with an appropriate-

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ly blocked galactose will result in formation of both a
type I structure [βGal(1→3)βGlcNAc-OR] and type II
structure [βGal(1→4)βGlcNAc-OR] which are readily
separated by conventional techniques including
5   chromatography.

Compound 16 is prepared by treating p-chloro-
thiophenol with 0.95 equivalents of potassium hydroxide
in ethanol followed by heating the solution to about
40-50°C and then adding about 0.5 equivalents of
10   compound 2 to the reaction solution. The reaction is
maintained at 40-50°C for about 1-2 hours and the
product 16 precipitates upon cooling the solution and
is recovered by filtration.

The synthesis of compounds 26 - 31 are
15   depicted in Figure 2 and are set forth in the examples
hereinbelow. In this figure, D-galactose pentaacetate
26 is produced by slurring D-galactose and about an
equimolar amount (e.g., about 1.1 equivalents) of
sodium acetate (NaOAc) in dichloroethane (DCE), heating
20   to reflux and adding at least 5 equivalents of acetic
anhydride (AcOAc) dropwise to the refluxing solution
(about 80-85°C) and then maintaining the reaction
system at this temperature for a sufficient period of
time (about 16-32 hours) to result in formation of
25   compound 26. This procedure optimizes the yield of
ß-D-galactose pentaacetate 26 and controls the exotherm
of heretofore known procedures.

After workup of the solution, the product is
treated with approximately equimolar amounts of benzyl
30   mercaptan (Ph-CH$_2$-SH) and from about 1-3 (preferably
two) equivalent of boron trifluoride etherate (BF$_3$·OEt$_2$)
in dichloromethane. The reaction conditions are not

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critical and the reaction is preferably conducted at
from about 0°C to about 30°C for a period abouut 6 to
16 hours to yield after crystallization from hot
methanol or hot isopropanol 55-65% of benzyl 2,3,4,6-
5   tetra-O-acetyl ß-D-thiogalactopryanoside, compound **27**.

     Deacetylation under Zemplen conditions
(sodium methoxide/methanol) leads to compound **28**.
Deacetylation reaction conditions are not critical and
the reaction is generally conducted at room temperature
10   for a period of from about 2 to about 15 hours. After
the deacetylation reaction is complete (as judged by
t.l.c.), the solution is neutralized with an acid ion
exchange resin, filtered and evaporated to dryness to
provide for compound **28**. The residue is crystallized
15   from hot acetone and the product is taken up in
dimethylformamide or acetonitrile and treated with from
1 to 2 equivalents (preferably 1.4 equivalents) of
benzaldehyde dimethyl acetal and about 0.25 to 3 weight
percent of p-toluenesulphonic acid (based on compound
20   **28**). The reaction conditions are not critical and
preferably the reaction is conducted at room
temperature and is generally complete in about 12 to 24
hours. After neutralization, the benzyl 4,6-O-
benzylidene ß-D-thiogalactopyranoside, **29**, is isolated
25   and crystallized from hot isopropanol.

     Benzyl 4,6-O-benzylidene-3-O-chloroacetyl-
ß-D-thiogalactopyranoside **30** is prepared by
chloroacetylation using from about 1 to 3 (preferably
2) equivalents of chloroacetylchloride which is added
30   to a dimethylformamide (DMF) solution containing benzyl
4,6-O-benzylidene ß-D-thiogalacto-pyranoside **29**. The
chloroacetylchloride is added dropwise while
maintaining the DMF solution at from about -40° to

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about -15°C (preferably at -25°C). Under these
conditions, it is unexpectedly been found that the use
of DMF permits selective chloroacetylation of compound
29 without the need for additional base. The reaction
5   is generally complete in about 10-24 hours.

Benzyl 4,6-O-benzylidene-3-O-chloroacetyl-β-
D-thiogalactopyranoside (compound 30) is benzoylated
with at least 1 equivalent (and preferably about 2
10   equivalents) of benzoyl chloride in a suitable solvent
containing a base (e.g., pyridine/methylene chloride)
with from about 0.1 to about 1 weight percent of
dimethylaminopyridine [DMAP] as a catalyst. The
reaction conditions are not critical and preferably the
15   reaction is conducted at from about 0°C to about 30°C
and for about 1 to about 4 hours (preferably room
temperature for 2 hours) to give crystalline benzyl
4,6-O-benzylidene 2-O-benzoyl-3-O-chloroacetyl-β-D-
thio-galactopyranoside, compound 31, in approximately
20   10-20% overall yield from galactose.

The advantage of this approach is that after
subsequent assembly the blocked intermediates will be
simply deblocked and modified by sulfation or
phosphorylation. The material is crystalline and the
25   process obviates the need for chromatography.

The sulfates and phosphates of the galactose
moiety of blocked Lewis^c-YR and LacNAc-YR can also be
made using compound 32 in the synthesis of these
compounds. This compound is made by direct
30   benzoylation of both the 2,3-hydroxyl groups of
compound 29. However, after deblocking, both the 2 and
3 hydroxyl groups of galactose are then available for
sulfation and phosphorylation and the selectivity is

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not as efficient. Selectivity can be improved by, for
example, conducting the sulfation reaction at a low
temperature (e.g., -50°C).

5   Compound **29** can be converted to the 2,3-.
dibenzoyl protected compound **32** in a manner similar to
that described above for the preparation of compound
31. In this case, 3-5 equivalents of benzoyl chloride
are generally employed.

10   Compounds **31** and **32** are converted to
compounds **33** and **32a** (shown in Figure 4) via known
methodology (Norberg et al.[26]) using bromine
tetraethylammonium bromide.

       Alternatively, compound **31** can be converted
to compound **34** by contacting compound **31** with 80%
15   acetic acid/water at approximately 50°C for about 1-2
hours. Compound **34** is then converted to compound **35** by
treatment with acetic anhydride/pyridine in
dichloromethane.

       In another embodiment, compound **32** is treated
20   with sodium cyanoborohydride and ceric chloride to
provide for the benzyl-2,3-O-dibenzoyl-4-O-benzyl-β-D-
thiogalactopyranoside (not shown). In turn, this
compound is chloroacetylated at the 6-hydroxyl group.
After formation of the Lewis[c]-OR or LacNAc-OR blocked
25   structures, the chloroacetyl group can be selectively
removed (as described above) and then either
phosphorylated or sulphated so as to provide for the 6-
phosphate or 6-sulfate derivative.

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2B. FORMATION OF TYPE I STRUCTURES HAVING SULFATE
     SUBSTITUTION AT THE 3 OR 6-POSITIONS OF GALACTOSE

        Figure 3A illustrates one method for the
preparation of 3-sulfated Lewis^c-OR compounds.
5 Specifically, in Figure 3A, compound 101, is prepared
by reacting N-acetylglucosamine-OR (e.g., compound 4 in
Figure 1) with $C_6H_5CH(OCH_3)_2$ in an acidic acetonitrile
or dimethylformamide (DMF) medium at from about 0° to
about 50°C over 12-48 hours to provide for the
10 4,6-diprotected benzylidine compound 101.

        About 1 equivalent of N-iodosuccinimide is
combined with about 1 equivalent of trifluoromethane-
sulfonic acid in methylene chloride containing
molecular sieves which remove any water present. The
15 reaction mixture is cooled to -50°C and then compound
101 is added followed by the addition of approximately,
1 to 1.1 equivalents of compound 32 (based on compound
101). The reaction is allowed to equilibrate to about
-20° to 0°C over about 1-3 hours. The reaction
20 solution is then quenched by cooling to -50°C followed
by the addition of triethylamine until neutral pH is
reached. The solution is filtered through Celite and
then washed with a saturated sodium bicarbonate
solution and water. The organic layer was dried and
25 stripped in vacuo to provide for fully protected
disaccharide 102.

        In this reaction, compound 32a or 112 can be
used in place of compound 32. Compound 112 is
analagous to compound 32a but has a 4,6-p-methoxy-
30 benzylidine protecting group on the galactose [prepared
from compound 28 using $(CH_3O)_2CH-C_6H_4-p-OCH_3$] instead of
the benzylidine protecting group of compound 32a.

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The benzoyl groups on disaccharide 102 are
removed under Zemplen conditions (NaOMe/MeOH) to
provide for disaccharide 103 having free hydroxyl
groups at the 2,3 positions of the galactose.
5   Disaccharide 103 is sulfated in DMF at about -30° to
-50°C using about 1.1 to 1.5 equivalents of sulfur
trioxide/pyridine complex to provide for the 3-sulfated
disaccharide 104 as the pyridinium salt. This product
contains some 2-sulfated and some 2,3-disulfated
10   material which can be separated by chromatography. The
selectivity of the sulfating step is improved by the
use of colder temperatures. Alternatively, compound
103 can be chloroacetylated under typical conditions to
provide for a mixture of the 2- and 3-chloroacetyl
15   protecting groups. This mixture can be separated by
chromatography and the resulting purified components
can be used to prepare 2- or 3-sulfated products
selectively, or for that matter, the 2-phosphorylated
and 2-OCHR$_{18}$COOH substituents (discussed below), both of
20   which find utility in this invention as
immunomodulating compounds.

Passage of a methanol solution of the
3-sulfated disaccharide pyridinium salt, 104, through
Na$^+$ ion exchange resin provided for the sodium salt,
25   105. Compound 105 was deblocked under conventional
conditions to provide for the 3-sulfated Lewis^c-OR
derivative, 106, not shown.

A differentially protected Lewis^c-OR
structure can be prepared by combining compound 5 with
30   compound 31 under suitable conditions to provide for a
fully blocked Lewis^c-OR structure having a 3-
chloroacetyl blocking group and a 2-benzoyl blocking
group on the galactose unit. This compound can then be

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selectively deblocked at the 3-position of the
galactose and then sulfated in the manner described
above to provide for the 3-sulfated blocked structure.
However, deprotection of this product may lead to the
5   generation of by products (e.g., the 2-NH$_2$ of the
GlcNAc). If necessary, these by products can be
separated by chromatography.

Figure 3B illustrates one method for
preparing the 6-sulfate Lewis^c-OR compound.
10   Specifically, compound 107 is prepared from compound
28 by treating compound 28 with p-anizaldehyde
dimethylacetal under conditions otherwise identical to
the preparation of compound 29. The resulting product
is benzoylated under conditions similar to those
15   employed to prepare compound 32. This compound is then
ring opened using sodium cyanoborohydride in acidic
medium in tetrahydrofuran which yields the free 4-OH
derivative which, in turn, is acetylated under typical
conditions to provide for compound 107. Compound 107
20   is then converted to the 1-α-bromo derivative using
Norberg[26] conditions (bromine, tetraethylammonium
bromide at 0°C in methylene chloride) to provide for
compound 108.

Compound 108 is then combined with compound
25   101 in the presence of methylene chloride, silver
carbonate (about 3 equivalents), silver triflate (about
0.1 equivalents) and molecular sieves. The reaction is
conducted at about 0°C to room temperature for about 5
to about 16 hours to provide for the fully protected
30   Lewis^c-OR derivative, compound 109. The p-methoxybenzyl
blocking group at the 6-position of the galactose unit
is selectively removed by contacting compound 109 with
dichlorodicyanoquinone (DDQ) in methylene chloride and

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a trace of water to provide for compound **110**. Compound
110 is then sulfated at the 6-position of the galactose
in DMF at about -50° to 0°C using about 1.1 to 1.5
equivalents of sulfur trioxide/pyridine complex to
5   provide for the 6-sulfated blocked Lewis^c-OR as the
pyridinium salt.

Passage of a methanol solution of this
sulfated product through a Na$^+$ ion exchange resin
provided for the sodium salt, compound **111**, which upon
10 deblocking provides for compound **121**.

2C.   FORMATION OF TYPE II STRUCTURES HAVING SULFATE
      SUBSTITUTION AT THE 3 OR 6-POSITIONS OF GALACTOSE

Figure 4 illustrates one method for the
preparation of intermediates useful in the preparation
15 of 3-sulfated LacNAc-OR compounds. Specifically, in
Figure 4, compound **7** and approximately 1.6-1.7
equivalents of compound **32a** are dissolved in
dichloromethane containing molecular sieves to which is
added about 1 equivalent (based on compound **7**) of 2,6-
20 di-t-butyl-4-methylpyridine. The reaction is stirred
for 30 minutes at room temperature and then cooled to
-50°C. An anhydrous toluene solution containing
approximately a slight excess (e.g., about 1.2
equivalents) of silver trifluoromethanesulfonate is
25 then added to the solution and the reaction was allowed
to warm to -15°C over 2 hours and maintained at that
temperature for an additional 5 hours.

After reaction completion, the reaction
system was worked up to provide a crude product of
30 compound **42**. This is then purified by conventional

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techniques such as column chromatography using silica
gel and toluene-ethyl acetate (1:1) as the eluant.

The benzoyl groups on the protected LacNAc-OR
42 are removed under Zemplen conditions to provide for
5   the LacNAc-OR derivative having free hydroxyl groups at
the 2,3 positions of the galactose. This disaccharide
is sulfated in DMF at about -30° to -50°C using about
1.1 to 1.5 equivalents of sulfur trioxide/pyridine
complex in the manner described above to provide for
10   the blocked 2-hydroxy-3-sulfated LacNAc-OR as the
pyridinium salt. This product contains some 2-sulfated
and some 2,3-disulfated material which can be separated
by chromatography. The selectivity of the sulfating
step is improved by the use of colder temperatures.

15   Alternatively, the 2,3-dihydroxy disaccharide
can be chloroacetylated under typical conditions to
provide for a mixture of the 2- and 3-chloroacetyl
protecting groups. This mixture can be separated by
chromatography and the resulting purified components
20   can be used to prepare 2- or 3-sulfated products
selectively.

Passage of a methanol solution of the 3-
sulfated LacNAc-OR pyridinium salt through Na$^+$ ion
exchange resin provides for the sodium salt and
25   conventional deblocking provides for the 3-sulfated
LacNAc-OR derivative.

Figure 4 also illustrates a differentially
blocked LacNAc-OR structure which can be used to
prepare 3-sulfated structures. Specifically, compound
30   7 and compound 33 are combined to form compound 37.
This is accomplished by dissolving compound 7 and

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approximately 1.5 equivalents of compound 33 in
dichloromethane containing molecular sieves to which is
added about 1 equivalent (based on compound 7) of
2,6-di-t-butyl-4-methylpyridine. The reaction is
5   stirred for 30 minutes at room temperature and then
cooled to -50°C. An anhydrous toluene solution
containing approximately a slight excess (e.g., about
1.2 equivalents) of silver trifluoromethane sulfonate
is then added to the solution and the reaction is
10   allowed to warm to -15°C over 2 hours and maintained at
that temperature for an additional 5 hours.

At this time, the molecular sieves are
removed by filtration by passing through celite and the
recove d solution is quenched by addition to a
15   saturated sodium bicarbonate solution. The organic
extract is then washed with water, with aqueous 0.5N
HCl, and then with water. The organic solution is then
dried and concentrated in vacuo to provide a crude
product, compound 37. This is then purified by
20   conventional techniques such as column chromatography
using silica gel and hexane-ethyl acetate (1:1) as the
eluant.

Compound 37 is then selectively deblocked at
the 3-position of the galactose and then sulfated in
25   the manner described above to provide for the 3-
sulfated blocked structure. However, deprotection of
this product may lead to the generation of by products
(e.g., the 2-NH_2 of the GlcNAc). If necessary, these
by products can be separated by chromatography.

30   The 6-sulfate derivative of LacNAc-OR is
prepared in the manner described above for the

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6-sulfate of Lewis^c-OR with the exception that
compounds **7** or **9** are used in place of compound **101** in
this reaction.

2D.   **FORMATION OF TYPE I AND II STRUCTURES HAVING**
5   **PHOSPHATE OR -CHR$_{18}$COOH SUBSTITUTION AT THE 3- OR**
         6-POSITIONS OF GALACTOSE

           Blocked Lewis^c-OR and blocked LacNAc-OR
compounds having a 2, 3- or 6-hydroxyl group (e.g.,
compound **103**) on the galactose unit can be can be
10   converted to the 2-, 3-, 6-phosphate group on the
galactose by reaction with diphenylphosphorochloridate
and 4-dimethylaminopyridine (1:1) in pyridine at 0·C[16].
The solution is allowed to warm to room temperature
over 0.5 hours and stirred for 15 hours. The resulting
15   compound is then hydrogenated under conventional
conditions (first with H$_2$ in EtOH with Pd on carbon for
15 hours and then with H$_2$ in EtOH with PtO$_2$ for 3 hours)
to provide for the phosphate derivative at the 2-, 3-or
6-position of galactose. Deprotection leads to the
20   modified Lewis^c-OR and LacNAc-OR compounds having a
phosphate substituent at the 2-, 3-, 6-position of
galactose which is purified and converted to its
disodium salt by contacting a solution of this compound
with a sodium form of Dowex 50 x 8.

25   In another embodiment, blocked Lewis^c-OR and
blocked LacNAc-OR compounds having a 2-, 3- or 6-
hydroxyl group (e.g., compound **103**) on the galactose
unit can then be alkylated by first adding an
appropriated base (e.g., silver oxide, barium
30   hydroxide, sodium hydride) and then adding benzyl
bromoacetate (BrCH$_2$COOBn) or other similar acetates
(e.g., BrCHR$_{18'}$COOBn -- where R$_{18'}$ is alkyl of from 1 to
7 carbon atoms or -COOBn) to the reaction medium in an

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appropriate solvent such as DMF. After reaction
completion, the benzyl ester(s) is (are) readily
removed by conventional hydrogenation techniques which
additionally removes the other benzyl protecting groups
5   and the benzylidine protecting group. Treatment with
sodium methoxide/methanol provides for a $-OCH_2COOH$ (or
$-OCHR_{18}COOH$ where R_{18} is alkyl of from 1 to 7 carbon
atoms or $-COOH$) substituted to the 2-, 3-, 6-position
of galactose.

10 2E. MODIFICATION ON THE 2 AND/OR 6 POSITIONS OF
                    GlcNAc

        The 2,6 positions of the GlcNAc unit can be
modified prior to coupling so as to provide for
Lewis^c-OR and LacNAc-OR structures modified at these
15 positions which are then further modified in the manner
described above to prepare the sulfated, phosphorylated
or $-CHR_{18}COOH$ derivatives. In any event, function-
alization of the GlcNAc unit at the 2,6 position is
generally at a point in the synthesis where the to-be
20 formed functional group does not interfere with any of
the further intended reactions. For example, if an R_1
functional group in GlcNAc-OR would interfere with the
coupling reaction with the blocked galactose, then the
functional group can either be introduced at the
25 disaccharide level or blocked at the monosaccharide
level (e.g., 2-amino groups are conventionally blocked
with as the N-trifluoroacetamido or the N-phthalimido
group) and later deblocked.

    i. Modification at the 2-position of GlcNAc
30   Modification at the 2-position of GlcNAc can
be accomplished by a variety of ways. For example, the

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known[8,9] 2-azido-2-deoxy-glucose-OR compound (prepared, for example, by azidonitration of 4,5,6-triacetylglucal) can be protected at the 6 position with a removable protecting group (i.e., $Si(C_6H_5)_2tBu$)

5   by conventional techniques[8,9] and then combined with an appropriate blocked galactose compound in the manner described above to provide for the blocked $\beta Gal(1 \rightarrow 3)GlcN_3$-OR and $\beta Gal(1 \rightarrow 4)GlcN_3$-OR derivatives which are readily separated by conventional techniques.

10   At the appropriate time during synthesis of the Lewis[c]-OR and LacNAc-OR structures, the azido group is reduced to an amino group which can be protected, for example, as N-trifluoroacetamido. In turn, the trifluoroacetamido group is removed at the appropriate

15   point in the synthesis thereby unmasking the amino group.

The amino group can also be derivatized by conventional methods to provide for $-NR_{11}C(O)R_{10}$, $-NHSO_3H$, $-N=C(R_{11})_2$, $-NHCH((R_{11})_2$, $-NHR_{12}$, and $-N(R_{12})_2$

20   groups. For example, the $-NH_2$ group can be reacted, using conventional techniques:
with a carboxylic acid, anhydride or chloride to provide for amides. Alternatively, the desired acid can be activated, as reported by Inazu et al[37] and then

25   reacted with the amino group. The carboxylic acid, anhydride, chloride, or activated acid is selected so as to provide for an R_{10} group (i.e., as part of the $-NR_{11}C(O)R_{10}$ substituent) which is hydrogen or alkyl of from 1 to 4 carbon atoms,

30   with an aldehyde or ketone (of from 1 to 4 carbon atoms) at controlled pH to form an imine $[-N=C(R_{11})_2]$ which upon reduction (e.g., with sodium cyanoboro-

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hydride) provides for an alkylamine substituent [i.e.,
-NHCH(R$_{11}$)$_2$] as reported by Bernotas et al.[38],

    with a cyclic carbonate such as ethylene carbonate
or propylene carbonate which ring opens upon reaction
5   with the amine to form a carbamate group having an
HO-alkylene-OC(O)NH- substituent where alkylene is from
2 to 4 carbon atoms as reported by Wollenberg et al.[39],
U.S. Patent No. 4,612,132,

    with a chloroformate [i.e., ClC(O)OR$_{13}$] in the
10   manner disclosed by Greig et al.[40]. In this case, the
chloroformate has an R$_{13}$ group which is alkyl of from 1
to 4 carbon atoms,

    with O=C(O-C$_6$H$_4$-pNO$_2$)$_2$ which leads to an activated
intermediate which is then reacted with an amine
15   (HNR$_{14}$R$_{15}$) to provide for ureas [-NHC(O)NR$_{14}$R$_{15}$] as
described by Piekarska-Bartoszewicz et al.[41],

    with trimethylamine, sulfur trioxide (SO$_3$) so as
to form the -NHSO$_3$H group as described by Petitou[27], and

    with derivatized formic acid or other materials to
20   form a formamide (-NH-CHO)[28] which can be further
functionalized to the isocyano (-N=C=O) and reduced to
the deoxy derivative by tributyltin hydride (Bu$_3$SnH)[28].

    Alternatively, the 2-deoxy (R$_2$ = H) and 2-
alkoxy glucose derivatives [i.e., derivatives of GlcNAc
25   where the NAc has been replaced by -H (deoxy) or by an
-OR$_{12}$ (alkoxy)] are prepared using a synthetic scheme
similar to that recited by Trumtez et al.[28]
Specifically, the known 3,4,6-triacylated 1,2-ortho
ester of glucose is deacylated under conventional
30   conditions to give the 1,2-ortho ester of glucose.
This compound is then converted to the 3,4,6-tribenzyl
1,2-ortho ester of glucose using conventional
techniques. The 1,2-ortho ester of the resulting

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compound is then opened by conventional techniques to
provide a protected glycosyl donor such as the
1-α-bromo-2-acetyl-3,4,6-tribenzyl derivative of
glucose. This 1-α-bromo derivative is then converted
5   to the glycoside (-OR) by conventional techniques and
the 2-acetyl group is then removed. The 2-position is
now ready for formation of the 2-deoxy by conventional
methods such as first treating with carbon disulfide
and methyl iodide in the presence of one equivalent of
10   a base to form the -C(S)SCH$_3$ derivative, followed by
reaction with tributyltin hydride) or for the
preparation of the 2-alkoxy. The remaining protecting
groups are removed so as to provide for 2-deoxyglucose
glycoside or a 2-alkoxyglucose glycoside which can then
15   be derivatized in the manner described above and
illustrated in Figure 1 without the need to form the
aglycon.

ii. Modification at the 6-Position of GlcNAc
As shown in Figure 6, the 6-deoxy derivative
20   of GlcNAc-OR is synthesized from a known benzylidene
ring blocked saccharide (8-methoxycarbonyloctyl-2-
acetamido-4,6-O-benzylidene-2-deoxy-β-D-gluco-
pyranoside)[29] which is protected at the 3-hydroxy
position with a removable benzoyl blocking group (Bz)
25   by reaction with benzoic anhydride in pyridine.
Further conversion of this compound by reaction with
N-bromosuccinimide and barium carbonate in carbon
tetrachloride (CCl$_4$) at 65°C leads to the 3,4-
dibenzoyl-6-bromo-GlcNAc-OR compound. This compound
30   is, in turn, converted to the 3,4-dibenzyl-6-deoxy-
GlcNAc-OR by reaction with (C$_4$H$_9$)$_3$SnH in the presence of
AIBN (azo bis-isobutyronitrile) at 110°C followed by
treatment with methanol/sodium methoxide. This
compound can then be deprotected by conventional

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techniques to provide for the 6-deoxyGlcNAc-OR
glycoside which can then be derivatized in the manner
described above and illustrated in Figure 1 without the
need to form the aglycon.

5   The 6-azido derivatives of GlcNAc-OR can be
prepared in the manner described in Figure 5.
Specifically, GlcNAc-OR, compound 87, is converted to
the p-methoxybenzylidine blocked compound 88 by
reaction with $(CH_3O)_2CH-C_6H_4-p-OCH_3$.   This compound is
10   then protected at the 3-hydroxyl position by reaction
with $4-CH_3O-C_6H_4-CH_2Br$ to provide for compound 89 where
X is $4-CH_3O-C_6H_4-CH_2-$.   Compound 89 is partially
deprotected at the 4 and 6 positions by reaction with
acetic acid (AcOH) in water at about 45°C to provide
15   for compound 90. The 6-mesylate, compound 91, is
prepared by reacting compound 90 with mesyl chloride in
pyridine (MsCl/py). The 6-azido derivative, compound
92, is then formed by reaction with sodium azide in
dimethylformamide (DMF) and removal of the 3-blocking
20   group with dichlorodicyanoquinone (DDQ) yields compound
93.

           The 6-mesyl compound 91 can also be
derivatized to any of a number of 6-substituents
including alkoxy substituents, and the like by well
25   known chemistry.

           The 6-azido compound 92 can be derivatized to
the 6-amino at an appropriate point in the synthesis of
the Lewis[c]-OR or LacNAc-OR analogues in the manner
described above. The 6-amino derivative can then be
30   further functionalized by conventional methods to
provide for $-NR_5C(O)R_4$, $-NHSO_3H$, $-N=C(R_5)_2$, $-NHCH(R_5)_2$,

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$-NHR_6$ and $-N(R_6)_2$. For example, the $-NH_2$ group can be reacted, using conventional techniques, with:

a carboxylic acid, anhydride or chloride to provide for amides. Alternatively, the desired acid

5   can be activated, as reported by Inazu et al[37] and then reacted with the amino group. The carboxylic acid, anhydride, chloride, or activated acid is selected so as to provide for an R_4 group (i.e., as part of the $-NR_5C(O)R_4$ substituent) which is hydrogen or alkyl of

10   from 1 to 4 carbon atoms,

with an aldehyde or ketone (of from 1 to 4 carbon atoms) at controlled pH to form an imine $[-N=C(R_5)_2]$ which upon reduction (e.g., with sodium cyanoboro-hydride) provides for an alkylamine substituent [i.e.,

15   $-NHCH(R_5)_2$] as reported by Bernotas et al.[38],

with a cyclic carbonate such as ethylene carbonate or propylene carbonate which ring opens upon reaction with the amine to form a carbamate group having an HO-alkylene-OC(O)NH- substituent where alkylene is from

20   2 to 4 carbon atoms as reported by Wollenberg et al.[39], U.S. Patent No. 4,612,132,

with a chloroformate [i.e., $ClC(O)OR_7$] in the manner disclosed by Greig et al.[40]. In this case, the chloroformate has an R_7 group which is alkyl of from 1

25   to 4 carbon atoms,

with $O=C(O-C_6H_4-pNO_2)_2$ which leads to an activated intermediate which is then reacted with an amine (HNR_8R_9) to provide for ureas $[-NHC(O)NR_8R_9]$ as described by Piekarska-Bartoszewicz et al.[41],

30   with trimethylamine, sulfur trioxide (SO_3) at pH 9.5 so as to form the $-NHSO_3H$ group as described by Petitou[27], and

with derivatized formic acid or other materials to form a formamide $(-NH-CHO)$[28] which can be further

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functionalized to the isocyano (-N=C=O) and reduced to
the deoxy derivative by tributyltin hydride (Bu₃SnH)[28].

The 6-alkoxy derivatives of GlcNAc can be
prepared in the manner described in Figure 6.

5   Specifically, GlcNAc-OR, compound 87, is reacted with
$C_6H_5CH(OCH_3)_2$ in an acidic medium in acetonitrile to
provide for the 4,6-diprotected benzylidine compound
94. In turn, compound 94 can be reacted with benzyl
(Bn) bromide and sodium hydride in the presence of

10   dimethylformamide at around 0°C to provide for a benzyl
protecting group at the 3-position, i.e., compound 95.
Deprotection at the 4,6 positions by contacting
compound 95 with acetic acid and water at about
80°-90°C provides for compound 96. Reaction of

15   compound 96 with dibutyltin oxide [(Bu)₂SnO] and R₆Br
provides for the 6-alkoxy compound 97. Conventional
deprotection of the benzyl group with hydrogen in
palladium/carbon yields compound 98.

In another embodiment, compound 94 can be

20   reacted with [C₆H₅C(O)]₂O in pyridine to provide for a
benzoyl protecting group (Bz) at the 3-position, i.e.,
compound 99. Reaction of compound 99 with N-bromo-
succinimide in carbon tetrachloride yields the 6-bromo
compound 100. Compound 100 can be reacted with

25   tributyltin hydride [(Bu)₃SnH] in toluene to provide
for the 6-deoxy compound 100b which after conventional
deprotection of the benzoyl groups with sodium
methoxide in methanol gives the 6-deoxy compound 100c.

The 6-SR₆ compounds are prepared from the 6-

30   mesyl derivative, compound 91, by reaction with
potassium thioacetate, $CH_3C(O)S^-K^+$, to give the
thioacetate derivative at the 6-position. This

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derivative is then treated with mild base to produce
the 6-SH derivative. The 6-SH can be reacted with an
alkyl halide (e.g., CH_3Br) to provide the $-SR_6$
derivatives which, in turn, can be partially or fully
5   oxidized to the 6-sulfone or the 6-sulfoxide
derivatives, $-S(O)R_6$ and $-S(O)_2R_6$ where R_6 is alkyl of
from 1 to 4 carbon atoms.

Figure 7 illustrates the preparation of 3-
hydroxy or 4-hydroxy blocked $GlcNH_2$-OR where the amino
10   group is protected as an N-phthalimido group.
Specifically, in Figure 7, compound 13 is prepared by
the methods described above. This compound is then
deacetylated by conventional techniques (sodium
methoxide/methanol) to provide for compound 14 which is
15   then benzylidenated under conventional techniques to
provide compound 66. Compound 66 is then treated with
benzyl chloride and sodium hydride in dimethylformamide
at about -20°C to 20°C to provide for compound 67. The
benzylidine group of compound 67 is then removed with
20   80% aqueous acetic acid at about 80°C for about 1-4
hours to provide for compound 68. This compound is
then selectively acetylated at the 6-position by use of
approximately equimolar amounts of acetyl
chloride/pyridine in dichloromethane at about -10°C to
25   provide for compound 69.

As is apparent, compound 69 is useful in
preparing $LacNH_2$ derivatives whereas compound 66 is
useful in preparing Lewis[x]-OR derivatives.

The 2- or 3-sulfate, phosphate or $-OCHR_{18}COOH$
30   substituted LacNAc structures can be converted to the
6-sialyl derivatives by use of the known
$\beta Gal(1\rightarrow4)\beta GlcNAc$ $\alpha(2\rightarrow6)$sialyltransferase in a manner

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similar to that described in the examples herein below.
The 6-sialyl derivatives of Lewis^c-OR can be prepared
in a manner similar to that of Ratcliffe et al.[12,23]
making the appropriate modifications to the blocking

5   groups to allow for subsequent substitution with a
sulfate, phosphate or -CHR$_{18}$COOH group at the 2- or 3-
positions of galactose.

C.   Utility

Without being limited to any theory, it is

10   believed that the modified Lewis^c-YR and LacNAc-YR
compounds disclosed herein affect the cell mediated
immune response in a number of ways. Specifically,
these compounds can inhibit the ability of the immune
response to become educated about a specific antigen

15   when the compound is administered simultaneously with
the first exposure of the immune system to the antigen.

Also, the modified Lewis^c-YR and LacNAc-YR
compounds disclosed herein can inhibit the secondary
immune response to an antigen in a sensitized mammal

20   when administered after second or later exposures of
the immune system to the same antigen. Additionally,
the modified Lewis^c-YR and LacNAc-YR compounds
disclosed herein can induce tolerance to antigens when
administered at the time of second or later exposures

25   of the immune system to the antigen.

The suppression of the inflammatory component
of the secondary immune response by the modified
Lewis^c-YR and LacNAc-YR compounds disclosed herein
requires administering such compounds after initiation

30   of the mammal's secondary immune response but at or
prior to one-half the period required for maximal
antigen induced inflammation. This criticality is

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disclosed in U.S. Patent Application No. 07/988,518
filed concurrently herewith as Attorney Docket No.
000475-045 and entitled "TIME DEPENDENT ADMINISTRATION
OF OLIGOSACCHARIDE GLYCOSIDES RELATED TO BLOOD GROUP
5   DETERMINANTS HAVING A TYPE I OR TYPE II CORE STRUCTURE
IN REDUCING INFLAMMATION IN A SENSITIZED MAMMAL ARISING
FROM EXPOSURE TO AN ANTIGEN" which application is
incorporated herein by reference in its entirety.

In this embodiment, the modified Lewis^c-OR
10 and LacNAc-OR compounds are preferably administered to
the patient at least about 0.5 hours after antigen
exposure, more preferably, at least about 1 to 10 hour
after antigen exposure, and still more preferably, from
about at least about 1 to 5 hours after antigen
15 exposure.

Similarly, in cell-mediated inflammatory
responses arising from injuries (e.g., adult
respiratory distress injury (lung injury),
administration of the Lewis^c-YR and LacNAc-YR is also
20 conducted after initiation of the immune response to
this injury but at or prior to one-half the period
required for maximal inflammation.

The modified Lewis^c-YR and LacNAc-OR
glycosides disclosed herein are effective in
25 suppressing cell-mediated immune responses including
cell-mediated immune response to an antigen (eg. the
inflammatory component of a DTH response) as well as in
suppressing cell-mediated inflammatory responses to
injury (e.g., lung injury) when administered at a
30 dosage range of from about 0.5 mg to about 50 mg/kg of
body weight, and preferably from about 0.5 to about 5
mg/kg of body weight. The specific dose employed is

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regulated by the particular cell-mediated immune
response being treated as well as by the judgment of
the attending clinician depending upon factors such as
the severity of the adverse immune response, the age
5   and general condition of the patient, and the like.
The modified Lewis^c-YR or LacNAc-YR analogues are
generally administered parenterally, such as
intranasally, intrapulmonarily, transdermally and
intravenously, although other forms of administration
10 are contemplated.

        In addition to providing suppression of a
mammal's secondary immune response to an antigen,
administration of the modified Lewis^c-YR and LacNAc-YR
compounds disclosed herein also imparts a tolerance to
15 additional challenges from the same antigen provided
that the compound is administered during the critical
period discussed above. In this regard, re-challenge
by the same antigen weeks after administration of the
modified Lewis^c-YR or LacNAc-YR compounds results in a
20 significantly reduced immune response.

        Administration of the modified Lewis^c-YR and
LacNAc-YR compounds disclosed herein simultaneously
with first exposure to an antigen (i.e., a
non-sensitized mammal) imparts suppression of a cell-
25 mediated immune response to the antigen and tolerance
to future challenges with that antigen. In this regard
the term "reducing sensitization" means that the
modified Lewis^c-YR or LacNAc-YR compound, when
administered to a mammal in an effective amount along
30 with a sufficient amount of antigen to induce an immune
response, reduces the ability of the immune system of
the mammal to become educated and thus sensitized to
the antigen administered at the same time as the

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modified Lewis^c-YR or LacNAc-YR compound. An
"effective amount" of this compound is that amount
which will reduce sensitization (immunological
education) of a mammal, including humans, to an antigen
5   administered simultaneously as determined by a
reduction in a cell-mediated response to the antigen
such as DTH responses as tested by the footpad
challenge test. Preferably the reduction in
sensitization will be at least about 20% and more
10 preferably at least about 30% or more. Generally,
modified Lewis^c-YR and LacNAc-YR compounds disclosed
herein are effective in reducing sensitization when
administered at a dosage range of from about 0.5 mg to
about 50 mg/kg of body weight, and preferably from
15 about 0.5 mg to about 5 mg/kg of body weight. The
specific dose employed is regulated by the
sensitization being treated as well as the judgement of
the attending clinician depending upon the age and
general condition of the patient and the like.
20 "Simultaneous" administration of the compound with the
antigen with regard to inhibiting sensitization means
that the compound is administered once or continuously
throughout a period of time within 3 hours of the
administration of an antigen, more preferably the
25 compound is administered within 1 hour of the antigen.

The methods of this invention are generally
achieved by use of a pharmaceutical composition
suitable for use in the parenteral administration of an
effective amount of a Lewis^c-YR or a LacNAc-YR
30 compound. These compositions comprise a
pharmaceutically inert carrier such as water, buffered
saline, etc. and an effective amount of a modified
Lewis^c-YR or LacNAc-YR compound so as to provide the
above-noted dosage of these compounds when administered

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to a patient. It is contemplated that suitable
pharmaceutical compositions can additionally contain
optional components such as a preservative, etc.

5   It is also contemplated that other suitable
pharmaceutical compositions can include oral
compositions, transdermal compositions or bandages
etc., which are well known in the art.

           It is also contemplated that mixtures of
10   these compounds can be used.
           The following examples are offered to
illustrate this invention and are not to be construed
in any way as limiting the scope of this invention.
Unless otherwise stated, all temperatures are in
15   degrees Celsius. Also, in these examples, unless
otherwise defined below, the abbreviations employed
have their generally accepted meaning:

Å	=	Angstroms
AB	=	AB pattern
ax	=	axial
bs	=	broad singlet
BSA	=	bovine serum albumin
^{13}C-n.m.r	=	C^{13} nuclear magnetic resonance
d	=	doublet
dd	=	doublet of doublets
ddd	=	doublet of doublets of doublets
DDQ	=	dichlorodicyanoquinone
DTH	=	delayed-type hypersensitivity
eq	=	equatorial
g	=	gram
^{1}H-n.m.r.	=	proton nuclear magnetic resonance
i.r.	=	infra red
kg	=	kilogram
L	=	liter
m	=	multiplet
mL	=	milliliter
q	=	quartet
s	=	singlet
t	=	triplet
t.l.c.	=	thin layer chromatography
U	=	Units
μm	=	microns

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AG 1 X 8 (formate form) = ion exchange resin AG 1 x 8
(formate form) available from Bio-Rad Laboratories,
Richmond, CA

5   Dowex 50W X 8 (H^+ form) = ion exchange resin Dowex 50 X
8 (H^+ form) available from Dow Chemical, Midland, MI

IR-120 resin (H^+ form) = amberlite resin available from
Rohm & Haas, Philadelphia, PA

IR-C50 resin (H^+ form) = ion exchange resin IR-C50 (H^+
form) available from Rohm & Haas, Philadelphia, PA

10   Commercially available components are listed by
manufacturer and where appropriate, the order number.
Some of the recited manufacturers are as follows:

Merck   = E. Merck AG, Darmstadt, Germany

Millipore = Millipore Corp., Bedford, MA.

15 Waters   = Waters Associates, Inc., Milford, MA.

        The following examples are divided into two
parts. The first part (part I) relates to the
synthetic procedures to make the recited compounds
whereas the second part (part II) relates to the
20 biological results.

Part I -- Synthetic Procedures

        Examples 1-18 illustrate syntheses of the
described compounds.

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EXAMPLE 1 --   Synthesis of Benzyl-2-O-benzoyl-4,6-O-
                benzylidene-3-O-chloroacetyl-ß-D-
                thiogalactopyranoside (compound 31)

Dry a 20 L stirred reactor equipped with reflux
condenser, heating mantle and 1 L addition funnel.
Charge to this reactor 10 L of dichloroethane. Begin to
stir the reactor then charge 1 kg D-galactose and 500 g
anhydrous sodium acetate to the dichloroethane. Heat
this slurry to reflux. Add dropwise 4 L of acetic
anhydride to the reaction mixture using the 1 L
addition funnel on the reactor. Reflux is to be
maintained during the 2-4 hour addition period.
Continue to stir and heat the mixture at reflux
overnight.

When the reaction is complete as determined by
t.l.c., turn off the heat to the reactor and add 250 mL
of water in slow dropwise fashion using the addition
funnel. This reaction is quite vigorous but is
controlled by slowing the addition of the water. Stir
the reaction for 1-2 hours. Charge 30 L of cold water
to a 50 L stirred reactor and begin stirring. Drain
the contents of the 20 L reactor into a 20 L
polyethylene pail and pour into the stirring ice water
in the 50 L reactor. Stir this mixture for twenty
minutes. Drain the lower organic layer into a 20 L
polyethylene pail. Extract the aqueous layer in the 50
L reactor with an additional 5 L of dichloromethane.
Combine the dichloromethane extract with the first
organic layer. Drain the aqueous layer to polyethylene
pails and discard as aqueous waste.

Return the combined organic layers to the 50 L
reactor and extract twice with 5 L portions of ice wat-
er for 10 minutes. Drain the organic layer to a clean
20 L polyethylene pail. Drain the aqueous to waste,
return the organic layer to the 50 L reactor, stir and
add 1 kg of anhydrous sodium sulfate. Stir for 1-2

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hours and then drain the solution into a clean 20 L
polyethylene pail and filter the solution using a 4 L
vacuum filtration set [or large Buchner attached to a
collector].

5   Concentrate the filtrate to 8 L then transfer into
a clean 20 L reactor equipped with stirrer, 1 L
addition funnel and cooling bath. Additional solvent
can be added if the level of the solution is below the
thermowell. Cool the organic solution to 0°C using a
10   cooling bath. Charge to this cool solution 724 g of
benzyl mercaptan. Add a total of 1.1 L of colorless
boron trifluoride etherate in slow dropwise fashion
over 2 hours using the 1 L addition funnel. Stir the
reaction 3-4 hours after the addition is complete
15   maintaining the temperature at 0°C. The reaction is
checked for completion by t.l.c. on silica gel. [The
reaction can be left to sit overnight].

The reaction mixture is drained into a clean 20 L
polyethylene pail. The 50 L reactor is charged with 15
20   L of saturated sodium carbonate solution. The 20 L
polyethylene pail is slowly transferred into the slowly
stirring carbonate solution at such a rate that the gas
evolution is not overly vigorous. Stir the solution
for 20 minutes then increase the rate of stirring.
25   When gas evolution ceases bubble air through the entire
solution for 24-36 hours. Drain the organic layer into
a clean 20 L polyethylene pail and store in a hood.
Extract the sodium carbonate solution with 3-5 L of
dichloromethane and drain this solution into the same
30   20 L polyethylene pail.

Once the smell has been reduced the organic
solution can be filtered using a 4 L vacuum filtration
set and the filtrate evaporated under reduced pressure
on the 20 L rotovap. 7 L of methanol is introduced
35   into the rotavap flask and the residue heated with the

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rotavap bath till the residue dissolves in the warm
methanol. The flask is rotated and allowed to cool.
Cool ice water is added to the rotavap bath and the
flask slowly rotated for several hours. The flask is
5   removed from the rotovap and the white crystalline
product filtered using a 4 L vacuum filtration set.
        The benzyl 2,3,4,6-tetra-O-acetyl-β-D-
thiogalactopyranoside (~1.3 kg) is charged into a clean
dry 20 L reactor with stirring motor and 7 L of dry
10   methanol is added to dissolve the material. The
solution is treated with 3 g of freshly surfaced sodium
and stirred for two hours. The reaction is checked by
t.l.c. on silica gel using a retained sample of the
benzyl 2,3,4,6-tetra-O-acetyl-β-D-thiogalactopyranoside
15   with 80:20 ethyl acetate: methanol (v/v) the eluant.
The absence of starting material indicates the reaction
is complete.
        50 g of fresh methanol washed H$^+$ ion exchange
resin is added, the reaction stirred for 15 minutes.
20   The pH is checked using pH paper to ensure a neutral
solution. The resin is filtered off under reduced
pressure and the methanol is removed under reduced
pressure using the 20L rotovap. To the residue, 5 L of
acetone is added to the 20 L flask and the solution
25   warmed to reflux. The residue dissolves and is allowed
to cool to room temperature at which time ice is added
to the bath, the solution rotated with cooling
overnight. 800-900g of benzyl β-D-
thiogalactopyranoside crystallizes and is filtered and
30   dried under vacuum.
        To 8 L of dry acetonitrile is added 800 g of
benzyl β-D-galactopyranose, 600 g of benzaldehyde
dimethyl acetal and 2-5 g of p-toluenesulphonic acid.
The solution is stirred at room temperature overnight.
35   The reaction progress is checked b t.l.c. When

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complete, the reaction is brought to pH 7 by the
addition of triethylamine. The volume of acetonitrile
is reduced to a minimum, 7 L of isopropanol is added
and the mixture is heated to near reflux. Most of the
5   product goes into the hot isopropanol after warming for
several hours. The mixture is cooled and ice added to
the bath and cooling continued overnight to give a
precipitate. After filtering and drying the
precipitate, 760 g of benzyl-4,6-O-benzylidene-ß-D-
10 thiogalactopyranoside is obtained.
      180 g of benzyl-4,6-O-benzylidene-ß-D-
thiogalactopyranoside was dissolved in dry DMF and
placed in a jacketed reactor. The reactor was cooled
using a recirculating cooling bath maintained at a
15 temperature of -25°C and treated dropwise with 108 g
of chloroacetyl chloride over 3 hours while stirring
the reaction mixture. · Stirring was continued 24 hours
at this temperature then the reaction was quenched into
several volumes of cold bicarbonate solution. The
20 product was extracted into methylene chloride, water
washed several times, dried over sodium sulphate and
evaporated to dryness. The product was crystallized
from isopropanol. Yield: 125 g of benzyl 4,6-O-
benzylidene-3-O-chloroacetyl-ß-D-thiogalacto-
25 pyranoside.
      5 g Benzyl 4,6-O-benzylidene-3-O-chloroacetyl-ß-D-
thiogalactopyranoside was benzoylated at room
temperature in methylene chloride/pyridine using 3
equivalents of benzoyl chloride and a catalytic amount
30 of dimethylaminopyridine. The solution is quenched
into cold sodium bicarbonate solution, the organic
layer is washed with saturated copper sulphate solution
to remove the pyridine the organic layer dried and
evaporated. The residue is taken up in hot isopropanol
35 and benzyl 4,6-O-benzylidene-2-O-benzoyl-3-O-

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chloroacetyl-ß-D-thiogalactopyranoside crystallizes
from solution. ^{1}H-n.m.r. (CDCl$_3$): δ = 7.96, 7.4 (2m,
15H, aromatic, 5.79 (t, 1H, H-2), 5.5 (s, 1H, CH), 5.2
(q, 1H, H-4, $J_{2,3}$ 9.9 Hz, $J_{3,4}$ 3.3 Hz), 4.5 (m, 2H), 4.4
5   (d, 1H), 3.99 (m, 5H), 3.55 (s, 1H).

Example 2 --   Synthesis of 4,6-O-benzylidene-2,3-di-O-
                benzoyl-ß-D-galactopyranosyl bromide
                (compound 32A)

       Benzyl-4,6-O-benzylidene-β-D-thiogalacto-
10   pyranoside (10 g) was dissolved in 100 mL
dichloromethane and 6.35 g of pyridine was added. To
the solution was added 9 g of benzoyl chloride in
dropwise fashion and after 1 hour, 50 mg of
dimethylaminopyridine was added to the solution and the
15   mixture was stirred for an addition 2 to 4 hours. The
progress of the reaction was checked by t.l.c. on
silica gel. Benzyl-4,6-O-benzylidene-2,3-di-O-benzoyl-
β-D-thiogalactopyranoside (compound 32) was isolated by
quenching the reaction mixture into saturated sodium
20   bicarbonate solution and washing the organic extract
with water, 5% copper sulfate solution, water, drying
and evaporating the solvent. The residue was
crystallized from isopropanol to give 10.7 g of
compound 32.
25   Compound 32, benzyl-4,6-O-benzylidene-2,3-di-O-
benzoyl-β-D-thiogalactopyranoside (9.89 g), was
dissolved in 100 mL of dichloromethane, cooled to 0°C,
and treated with a solution of bromine (2.85 g) in 10
mL of dichloromethane. After 15 minutes, 1.8 grams of
30   tetraethylammonium bromide was added to the mixture and
the mixture stirred for 2-3 hours at room temperature
(followed by t.l.c. on silica gel). A small quantity
of cyclohexane was added to quench excess bromine and
the reaction mixture was quenched into cold saturate

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sodium bicarbonate solution, washed with water, dried
and volume of the solution reduced to 30 mL. This
dichloromethane solution of compound **32a** was used
directly in the synthesis of compound **42** without
5   further isolation and/or purification.

Example 3 --   Synthesis of 8-methoxycarbonyloctyl-2-
                acetamido-4,6-di-O-benzylidene-2-deoxy-
                ß-D-glucopyranoside
                (Compound 5)·

10   A 20L glass reactor was charged with 8 L of
dichloroethane, 1 L of acetic anhydride and 1 kg of
anhydrous sodium acetate. To the stirring mixture was
added 1 kg of glucosamine hydrochloride and the mixture
was brought to reflux. A further 3.5 L of acetic
15   anhydride was added dropwise to the refluxing solution
over 3-4 hours and the solution maintained at reflux
for 36 hours. During the last hour of reflux 200 mL of
water was added dropwise to the solution. The reaction
was then cooled and added to 35 L of ice water in a 50
20   L stirred reactor. The organic layer was removed and
then water washed a second time with an additional 20 L
of water. The organic layer was dried over sodium
sulphate, filtered, and saturated with anhydrous
gaseous HCl for 2 hours. The reaction was allowed to
25   sit for 6 days being saturated with HCl for 1 hour
every second day. 2-acetamido-2-deoxy-3,4,6-tri-O-
acetyl-ß-D-glucopyranosyl chloride was isolated by
quenching into ice cold sodium bicarbonate solution.
The organic layer was dried over sodium sulphate and
30   evaporated to a brown solid.
     Four hundred grams of 2-acetamido-2-deoxy-3,4,6-
tri-O-acetyl-ß-D-glucopyranosyl chloride was dissolved
in 2 L of anhydrous dichloromethane containing 200 g of
activated molecular sieves. 266 g of 8-

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methoxycarbonyloctanol was charged to the reaction
mixture along with 317 g of mercuric cyanide. The
solution was stirred rapidly at room temperature for 24
hours. After checking for reaction completion by t.l.c.
5   the reaction mixture was filtered through a buchner
funnel of silica and the organic layer washed twice
with water, twice with a 5% solution of potassium
iodide and twice with a saturated solution of sodium
bicarbonate. The solution was dried over sodium
10   sulphate and evaporated to dryness. The residue was
taken up in anhydrous methanol and treated with 1 g of
freshly cut sodium then stirred at room temperature
overnight. The solution of 8-methoxycarbonyloctyl 2-
acetamido-2-deoxy-ß-D-glucopyranoside was neutralized
15   with acid ion exchange resin and filtered and
evaporated to yield 218 g of product after
crystallization from isopropanol /diisopropyl ether.
       Two hundred grams of 8-methoxycarbonyloctyl 2-
acetamido-2-deoxy-ß-D-glucopyranoside was dissolved in
20   1.2 L of anhydrous dimethylformamide and treated with
169 mL of dimethoxytoluene (benzylaldehyde dimethyl
acetal) and 1-2 g of p-toluenesulphonic acid. The
reaction was stirred and heated to 40°C for 5 hours,
then checked for completion by t.l.c. When the
25   reaction appears complete the mixture was neutralized
with triethylamine and quenched into several volumes of
ice water, extracted into dichloromethane and
backwashed several times with water. The organic layer
was dried over sodium sulphate, evaporated to dryness
30   and taken up in hot isopropanol. After cooling 8-
methoxycarbonyloctyl-2-acetamido-4,6-O-benzylidene-2-
deoxy-ß-D-glucopyranoside precipitates. It is filtered
and dried to yield 106 g of product. ^{1}H-n.m.r.
(CDCl$_3$): δ = 7.41 (m,5H, aromatic), 6.11 (d, 1H, NH),

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5.5 (s, 1H, CH), 4.63 (d, 1H, H-1, $J_{1,2}$ 7.4 Hz), 2.29
(t, 2H), 1.99 (s, 3H, Ac), 1.58 (m, 4H), 1.29 (bs, 8H).

Example 4   --   Synthesis of 8-Methoxycarbonyloctyl 2-
                 acetamido-3-O-p-methoxybenzyl-4,6-O-
5   benzylidene-ß-D-glucopyranoside
                 (compound 6).

        To a stirred solution of compound 5 (17.5 g, ~3
mmol) in dry dichloromethane (100 mL) and catalytic
amount of p-toluenesulfonic acid (0.25 to 3 weight
10 percent based on compound 5) was added dropwise a
solution of p-methoxybenzyl trichloroacetimide (10 g in
25 mL CH_2Cl_2).   The reaction mixture was stirred at room
temperature overnight.   Triethylamine was added to
quench the reaction, the organic layer was washed with
15 sodium bicarbonate solution and the organic layer dried
and evaporated to dryness,   Crystallization in hot
ethanol gave 20 g of the desired product. ^{1}H-n.m.r.
(CDCl$_3$): δ 7.56-6.90 (m, 9H, aromatic), 5.60 (d, 1H,
NH), 5.30 (s, 1H, PhCH), 4.94 (d, 1H, $J_{1,2}$ 8.0Hz, H-1),
20 3.80 (s, 3H, CH_3), 3.60 (s, 3H, CH_3Ph), 2.30 (t, 2H,
CH_2CO), 1.90 (s, 3H, AcNH), 1.80-1.10 (m, 12H, $(CH_2)_6$).

Example 5 --   Synthesis of 8-Methoxycarbonyloctyl 2-
               acetamido-2-deoxy-3-O-p-methoxybenzyl-6-
               O-benzyl-2-ß-D-glucopyranoside (compound
25   7)

        To a stirred solution of compound 6 (15.0 g, ~3
mmol) in 200 mL of dry THF were added, 11.0 g of sodium
cyanoborohydride, 10 g of molecular sieves 4Å and 5 mg
of methyl orange.   The solution was cooled to -10°C and
30 then ethereal hydrochloric acid was added dropwise
until the solution remained acidic.   On completion of
the reaction, it was diluted with dichloromethane (200
mL), filtered through celite and washed successively

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with aqueous sodium bicarbonate (2 x 100 mL) and water
(2 x 100 mL) and then the solvent dried and evaporated
to give a syrup. Purification of the mixture on column
chromatography using silica gel as adsorbent and
5   eluting with hexane:ethyl acetate:ethanol (20:10:1)
gave 7 in 70% yield. ^{1}H-n.m.r. (CDCl$_3$): δ 7.40-6.90(m,
9H, aromatic), 5.70(d, 1H, NH), 4.64(d, 1H, $J_{1,2}$ 8.0Hz,
H-1), 3.86(s, 3H, CH$_3$O), 3.68(s, 3H, CH$_3$OPh), 2.30(t,
2H, CH$_2$CO), 1.90(s, 3H, NHAc), 1.80-1.10(m, 12H,
10   (CH$_2$)$_6$).

Example 6   --   Synthesis of 8-Methoxycarbonyloctyl 2-
                 acetamido-2-deoxy-3-O-p-methoxybenzyl-4-
                 O-(4,6-O-benzylidene-2,3-O-dibenzoyl-ß-
                 D-galactopyranosyl)-6-O-benzyl-2-deoxy-
15   ß-D-glucopyranoside (compound 42)

A solution of compound 7 (10.61 g, 19.7 mmol) and
compound 32A (1.6-1.7 equivalents based on compound 7)
and 2,6-di-t-butyl-4-methyl pyridine (3.11 g, 15.2
mmol) in 250 L of dichloromethane and 40 g of molecular
20   sieves (4Å) was stirred at room temperature for 30
minutes, and then cooled to -50°C under nitrogen. A
dry solution of silver triflate (4.47 g, 17.3 mmol) in
toluene (40 mL) was added to the stirred mixture. The
mixture was warmed to -15°C during two hours and kept
25   at -15°C for an additional 5 hours. At the end of
which the mixture was warmed to room temperature and
stirred overnight. 3 mL of pyridine and 250 mL of
dichloromethane were added to the mixture and was
filtered over celite, filtrate was washed with
30   saturated aqueous sodium hydrogen carbonate (200 mL)
and then with water (200 mL), aqueous hydrogen chloride
(0.5N, 200 mL) and water (200 mL), concentrated in
vacuo.   6.0 g of compound 8 was crystallized as white
crystals from ethyl acetate-diethyl ether-hexane. The

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mother liquor was concentrated, purified over
chromatography (300 g silica gel, toluene:ethyl
acetate, (1:1) to give 4.5 g pure compound **42**. Total
yield was 10.5 g (68%). Rf 0.48

5   (methanol:dichloromethane, 4:96). ^{1}H-n.m.r. (CDCl$_3$):
δ 5.80(t, 1H, $J_{2',3'}$ 11.0Hz, H-2'), 5.52(s, 1H, CHPh),
5.25(dd, 1H, $J_{3,4}$ 4.0Hz, H-3'), 4.88(d, 1H, $J_{1',2'}$
11.0Hz, H-1'), 4.70(d, 1H, $J_{1,2}$ 9.0Hz, H-1), 3.78(s, 2H,
CH$_3$O), 3.64(s, 3H, CH$_3$OPh).

10   Example 7   --   Synthesis of 2-O-benzoyl-4,6-O-
                       benzylidene-3-O-chloroacetyl-α-D-
                       galactopyranosyl bromide (compound **33**)

         Compound **32**, benzyl 4,6-O-benzylidene-2-O-benzoyl-
      3-chloroacetyl-β-D-thiogalactopyranoside (8.87 g) was
15   dissolved in 100 mL of dichloromethane, cooled to 0°C
      and treated with a solution of bromine (2.7 g) in 10 mL
      of dichloromethane. After 15 minutes, 1.7 g of
      tetraethylammonium bromide was added to the mixture and
      the mixture stirred for 2 to 3 hours at room
20   temperature (followed by t.l.c. on silica gel). A
      small quantity of cyclohexene was added to quench
      excess bromine and the reaction mixture was quenched
      into cold saturate sodium bicarbonate solution, washed
      with water, dried, and the volume of the solution
25   reduced to 30 mL so as to provide a dichloromethane
      solution of compound **33**. This solution was used
      directly in the synthesis of compound **37**.

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Example 8 --   Synthesis of 8-methoxycarbonyloctyl 2-
                acetamido-4-O-(2'-O-benzoyl-4',6'-O-
                benzylidene-3'-O-chloroacetyl-ß-D-
                galactopyranosyl)-6-O-benzyl-2-deoxy-3-
5   O-p-methoxybenzyl-ß-D-gluco-pyranoside
                (compound 37)

        A solution of the compound 7 (5.0 g, 0.9 mmol) and
compound 33 (1.4 to 1.5 equivalents -- from example 7)
and 2,6-di-t-butyl-4-methyl pyridine (1.78 g, 1.0 mmol)
10   in 50 mL of dichloromethane and 20 g of molecular
sieves (4Å) was stirred at room temperature for 30
minutes, and then cooled to -50°C under nitrogen. A
dry solution of silver triflate (3.3 g, 1.5 mL) in
toluene (10 mL) was added to the stirred mixture. The
15   mixture was warmed to -15°C over two hours and kept at
-15°C for an additional 5 hours, then allowed to warm
to room temperature and stirred overnight. 1 mL of
pyridine and 100 mL of dichloromethane were added to
the mixture and it was filtered over celite, the
20   filtrate was washed with aqueous sodium bicarbonate
(100 mL) and then with water (100 mL), aqueous hydrogen
chloride (0.5 N, 100 mL) and water (100 mL), then
concentrated in vacuo. Purification of the crude
mixture on column chromatography with silica gel as
25   adsorbent eluted with hexane:ethyl acetate (1:1) gave
5.2 g of pure compound 37. ^{1}H-n.m.r. (CDCl$_3$):
δ 5.85(d, 1h, NH), 5.62(t, 1H, $J_{2',3'}$ 10.8Hz, H-2'),
5.52(s, 1H-CH-benzylidene), 5.08 (dd, 1H, $J_{3',4'}$ 4Hz,
H-3'), 4.85 (d, 1H, $J_{1',2'}$ 11.0Hz, H-1'), 4.68 (d, 1H,
30   $J_{1,2}$ 9.0Hz, H-1), 3.72 and 3.64 (2s, 6H, OC$\underline{H}_3$ and
COOC$\underline{H}_3$); ^{13}C-n.m.r.: 159.0(aromatic c-p-methoxyl)
165.15(c=0, chloroacetyl), 167.12(c-0, acetyl),
174.2(c=0, $\underline{C}$OOCH$_3$), 99.64(c-1), 100.26(c-1'),
101.0(PhC$\underline{H}$).

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Example 9 --   Synthesis of 2-deoxy-2-phthalimido-
                1,3,4,6-tetra-O-acetyl-β-D-
                glucopyranoside (compound 1)

5   (D+) Glucosamine hydrochloride (100 g, 0.46 mol)
was added to a solution of sodium methoxide in methanol
which was prepared from equimolar amount of sodium
metal in methanol (0.5 L). The resultant mixture was
treated with equimolar equivalent of phthalic anhydride
and triethylamine (80 mL). The mixture was then
10   stirred for 2 hours, filtered and the solid was dried
in vacuum for 12 hours. The dry solid was dissolved in
pyridine (300 mL) and treated with acetic anhydride
(200 mL, 2.1 mol). The mixture was stirred at room
temperature for 48 hours and then quenched in an ice-
15   water mixture, and the resultant precipitate was
filtered, concentrated and crystallized from
diethylether to 98.3 g (45%) of the title compound.
^{1}H-n.m.r. (CDCl$_3$): δ 7.75 (m, 4h, aromatic), 6.45 (d,
1H, H-1, $J_{1,2}$ 9.0Hz), 5.85 (t, 1H), 5.15 (t, 1H), 4.4
20   (t, 1H), 4.3 (q, 1H), 4.1 (q, 1H), 4.00 (m, 1H), 2.05,
2.00, 1.95, 1.80 (4s, 12H, 4Ac). ^{13}C-n.m.r. (CDCl$_3$)
δ 89.7 (C-1), 72.6, 70.5, 68.3 (3C, C-3, C-4, C-5),
61.45 (C-6), 53.42 (C-2).

Example 10 --   Synthesis of 2-deoxy-2-phthalamido-
25   3,4,6-tri-O-acetyl-β-D-glucopyranosyl
                bromide (compound 12)

        2-deoxy-2-phthalamido-1,3,4,6-tetra-O-
acetyl-β-D-glucopyranoside 1 (20g, 41.9mmol) was
treated with hydrogen bromide solution in acetic acid
30   (30%, 200mL) and stirred at room temperature for 2 hrs.
The mixture was then poured into an ice water mixture
and extracted with dicloromethane. The extract was
washed with NaHCO$_3$ solution and water followed by MgSO$_4$
drying. The mixture is filtered, dried and

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concentrated in vacuo to give compound **12** as a dry
syrup (compound **12**)

Example 11 --   Synthesis of Ethyl 2-deoxy-2-
                 phthalimido-3,4,6-tri-O-acetyl-ß-D-
5   glucopyranoside (compound **13**)

    2-Deoxy-2-phthalamido-3,4,6-tri-O-acetyl-β-D-
glucopyranosyl bromide (compound **12**) from example 16
was taken up in dry ethanol and treated directly with
dry ethanol (200 mL), mercuric cyanide (13.7 g. 55
10   mmol) and stirred at room temperature for 48 hr. The
mixture was then filtered and concentrated. The
residue was taken up in 200 mL of dichloromethane and
washed with a solution of 10% potassium iodide, 5%
sodium bicarbonate, water, dried over MgSO$_4$ and
15   concentrated to a syrup.

Example 12 -- Synthesis of Ethyl 2-deoxy-2-
               phthalimido-ß-D-glucopyranoside
               (Compound **14**)

    Ethyl 2-deoxy-2-phthalamido-3,4,6-tri-O-acetyl-β-
20   D-glucopyranosyide (compound **13**) from example 17 was
taken up in 100 mL of dry methanol and treated with 100
mg of sodium metal. The solution was stirred at room
temperature for 24 hours and then neutralized with
Amberlite [R-120(H+)] resin, filtered, and evaporated
25   to dryness in vacuo. This compound was used in the
preparation of compound **15** and compound **66**.

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Example 13 --   Synthesis of Ethyl 2-deoxy-2-
                 phthalimido-6-O-benzyl-ß-D-
                 glucopyranoside (Compound 15)

Compound 14 (2.1 g, 6.23 mmol) was taken up in 100
mL of toluene. To it was added bis(tributyl tin) oxide
(2.22 mL, 4.35 mmol) and tetrabutylammonium bromide
(0.983 g, 3.05 mmol). The mixture was heated at 150°C
for 4 hours and then toluene (50 mL) was distilled off
from the mixture. The reaction mixture was cooled to
room temperature and benzyl bromide (2.17 mL, 18.27
mmol) was added and the reaction heated to 110°C for 36
hours. Toluene was evaporated and the residue taken up
in ethyl acetate (22 mL), washed successively with
aqueous sodium bicarbonate, saturated sodium chloride
solution and water. The organic layer was dried and
evaporated to dryness to give a crude solid.
Purification by column chromatography on silica gel
gave a crystalline solid 15 (1.4 g, 70%). ^{1}H-
n.m.r.(CDCl$_3$) δ 7.3-8.1 (9H, aromatic), 4.5 (dd, 2H,
C$\underline{H}_2$Ph), 5.18 (d, 1H, $J_{1,2}$ 10.0Hz, H-1), 4.36 (dd, 1H,
H-3), 4.25 (dd, H, $J_{2,1}$ 10.0Hz, $J_{2,3}$ 8.0Hz, H-2) and
1.0(t, 3H, CH$_3$).

Example 14 --   Synthesis of Ethyl 2-acetamido-6-O-
                 acetyl-3-O-benzyl-2-deoxy-ß-D-
                 glucopyranoside

A solution of compound 90 (described below-2 g,
4.68 mmol) in aqueous acetic acid (80%, 150 mL) was
heated at 80°C for 2 hours. The mixture then was
evaporated and the resultant solid was dried over P$_2$O$_5$
in high vacuum. The dry solid was selectively
acetylated with acetyl chloride (0.33 mL, 4.7 mmol) and
pyridine (10 mL) in dichloromethane (100 mL) at 10°C
to 5°C. The mixture was then diluted with
dichloromethane (50 mL), washed with aqueous NaHCO$_3$,

dried over MgSO$_4$ and evaporated. The residue was
chromatographed on a silica gel column using EToAc:
hexanes, 3:1 (v:v) as eluant to give 0.82 g (46%) of
the title compound: ^{1}H-n.m.r. (300 MHz, CDCl$_3$)

5 δ7.3(m, 5H, aromatic), 5.67(bs, 1H, NH), 4.86(d, 1H,
H-1), 4.75(m, 2H), 4.48(q, 1H), 4.27(d, 1H), 4.1(t,
1H), 3.85(m, 1H), 3.5(m, 3H), 3.16(m, 1H), 2.70(bs, 1H,
OH), 2.1(s, 3H, Ac), 1.9(s, 3H, Ac), 1.18(t, 3H, CH$_3$),
^{13}C-n.m.r. (CDCl$_3$): δ 99.45(C-1), 79.85, 74.5(CH$_2$ph),

10 73.7, 71.09, 65.25 (C-6), 63.36(CH$_2$-), 57.7(C-2),
23.6(Ac), 20.86(Ac), 15.06(CH$_3$).

Example 15 --   Synthesis of Ethyl 6-O-acetyl-3-O-
                 benzyl-2-deoxy-2-phthalimido-β-D-
                 glucopyranoside (compound 69)

15   A solution of ethyl 2-deoxy-2-phthalimido-β-D-
glucopyranoside (compound 14) from Example 12 was taken
up in dry acetonitrile (100 mL) and treated with
benzaldehyde dimethylacetal (9.6 g) and a catalytic
amount of p-toluenesulphonic acid (100 mg). The

20 mixture was stirred for 17 hours at room temperature
and then neutralized to pH 7 with triethylamine. The
mixture was evaporated and crystallized from hot
hexanes to give 12.7 grams of ethyl 4,6-O-benzylidene-
2-deoxy-2-phthalimido-β-D-glucopyranoside compound 66.

25   Compound 66 (10 g) was dissolved in dry
dimethylformamide (DMF) at -5°C and treated with 1.1 g
(46.6 mol) sodium hydride and benzyl bromide (5.46 mL,
22 mmol). The mixture was stirred at 0°C for 2 hours
and then treated slowly with 20 mL methanol then slowly

30 brought to room temperature and treated with HCl (1N)
to pH 7 and then extracted three times with
dichloromethane. The organic layer was dried over
anhydrous magnesium sulfate then filtered, concentrated
to dryness and taken up in hot ethanol to give 7.2 g of

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compound **67**. Compound **67** (5.43 g, 10.50 mmol) in
aqueous acetic acid (80%, 200 mL) was heated at 80°C
for 2 hours. The mixture was evaporated and the
resultant solid was dried over P_2O_5 in high vacuum. The
5   dry solid was selectively acetylated with acetyl
chloride (0.8 mL, 11.0 mmol) and pyridine (10 mL) in
dichloromethane (200 mL) at -10°C to 0°C. The mixture
was then diluted with dichloromethane (1 0 mL), washed
with aqueous $NaHCO_3$, dried over $MgSO_4$ and evaporated.
10 The residue was chromatographed on a silica gel column
using EtOAc:hexane, 1:2 (v:v) as eluant to give 3.5 g
(71%) of the compound **69**: ^{1}H-n.m.r. (300 MHz, $CDCl_3$):
δ 7.7(m, 4H, aromatic), 7.0(m, 5H, aromatic), 5.16(d,
1H, H-1), 4.7(d, 1H), 4.5(m, 2H), 4.2(m, 3H), 3.8(m,
15 1H), 3.6(m, 2H), 3.45(m, 1H), 2.9(bs, 1H, OH), 2.1(s,
3H, Ac), 1.95(t, 3H, CH_3). ^{13}C-n.m.r. ($CDCl_3$):
δ 98.09(C-1), 78.45, 74:5, 73.9, 71.7, 65.1, 63.1,
55.5, 20.87 (Ac), 14.92 (CH_3).

Example 16 --   Synthesis of Ethyl 6-O-acetyl-3-benzyl-
20   2-deoxy-2-phthalimido-4-O-(2,3,4,6-
                  tetra-O-acetyl-ß-D-galactosyl)-ß-D-
                  glucopyranoside (compound **70**)

To a stirred solution of compound **9** (80 mg, 0.17
mmol) in dichloromethane (10 mL) containing molecular
25 sieves (3A°, 1 g), 2,6-di-tert-butyl-4-methyl-pyridine
(45 mg, 0.22 mmol) and silver triflate (57 mg, 0.22
mmol) was added, at 30°C under nitrogen, 2,3,4,6-
tetra-O-acetyl-α-D-galactosyl bromide in
dichloromethane (5 mL). The mixture was stirred at
30 this temperature for 1 h and then warmed up to 5°C over
2h. The mixture was then diluted with dichloromethane
(10 mL), filtered and the insoluble material was washed
with dichloromethane (5 mL). The combined filtrates
were washed with saturated aqueous sodium hydrogen

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carbonate and water, dried over MgSO$_4$, and
concentrated. The residue was chromatographed on a
silica gel column using ethyl acetate: hexanes, 1:2
(v:v) as eluant to give 120 mg (80%) of the title

5   compound: ^{1}H-n.m.r. (300 MHz, CDCl$_3$): δ 7.68, 6.96(2m,
9H, aromatic), 5.3(m, 2H), 5.13(d, 1H, H-1´, J$_{1´,2´}$
8.0Hz), 4.99(q, 1H), 4.82(d, 1H), 4.62(d, 1H, H-1, J$_{1,2}$
7.7Hz), 4.54(d, 1H), 4.42(d, 1H), 4.3(q, 1H), 4.15(m
,2H), 3.99(m, 2H), 3.87(m, 2H), 3.72(m, 2H), 3.46(m,

10   1h), 2.15, 2.12, 2.09, 2.00, 1.98(5s, 15H, 5XAc),
1.00(t, 3H, CH$_3$).
^{13}C-n.m.r. (CDCl$_3$): δ 101.2, 97.8(C-1, C-1´),
14.85(CH$_3$).

        In the following examples, unless indicated

15   otherwise, R = -(CH$_2$)$_8$CO$_2$CH$_3$

Example 17 --   Synthesis of 8-Methoxycarbonyloctyl 3-O-
                (4,6-O-benzylidene-3-O-sulfo-β-D-
                galactopyranosyl)-2-acetamido-4,6-O-
                benzylidene-2-deoxy-β-D-glucopyranoside
20   (compound 105)

        The title compound was prepared by first
generating 8-methoxycarbonyloctyl 3-O-(2,3-di-O-
benzoyl-4,6-O-benzylidene-β-D-galactopyrnosyl)-2-

25   acetamido-4,6-O-benzylidene-2-deoxy-β-D-glucopyranoside
which, in turn, was generated by coupling the 8-
methoxycarbonyloctyl 2-acetamido-4,6-O-benzylidene-2-
deoxy-β-D-glucopyranoside and compound 32, the
synthesis of which is exemplified in example 2 above.

30   The 8-methoxycarbonyloctyl 2-acetamido-4,6-O-
benzylidene-2-deoxy-β-D-glucopyranoside can be prepared
by reacting N-acetylglucosamine-OR (e.g., compound 4 in
Figure 1) with about 1.5 equivalents of C$_6$H$_5$CH(OCH$_3$)$_2$ in
an acidic (p-toluene sulfonic acid) acetonitrile or

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dimethylformamide (DMF) medium at from about 0° to
about 50°C over 6-48 hours to provide for the 4,6-O-
protected benzylidine compound.

Coupling of compound 32 with the
5   8-methoxycarbonyloctyl 2-acetamido-4,6-O-benzylidine-2-
deoxy-β-D-glucopyranoside ("compound A") can be
achieved by first combining about 1 equivalent of N-
iodosuccinimide with about 1 equivalent of
trifluoromethanesulfonic acid in methylene chloride
10   containing molecular sieves which remove any water
present. The reaction mixture is cooled to -50°C and
then compound A is added followed by the addition of
approximately, 1 to 1.1 equivalents of compound 32
(based on compound A). When large amounts of
15   trifluoromethanesulfonic acid are employed, the
reaction is preferably cooled to -50°C prior to the
addition of the trifluoromethanesulfonic acid.

The reaction is allowed to equilibrate to
about -20° to 0°C over about 1-3 hours. The reaction
20   solution is then quenched by cooling to -50° followed
by the addition of triethylamine until neutral pH is
reached. The solution is filtered through Celite and
then washed with a saturated sodium bicarbonate
solution and water. The organic layer was dried and
25   stripped in vacuo to provide for 8-methoxycarbonyloctyl
3-O-(2,3-di-O-benzoyl-4,6-O-benzylidene-β-D-
galactopyranosyl)-2-acetamido-4,6-O-benzylidine-2-
deoxy-β-D-glucopyranoside ("compound B").

The benzoyl groups on compound B can be
30   removed under Zemplen conditions (NaOMe/MeOH) to
provide for 8-methoxycarbonyloctyl 3-O-(4,6-O-

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benzylidene-β-D-galactopyranosyl)-2-acetamido-4,6-O-
benzylidene-2-deoxy-β-D-glucopyranoside ("compound C").

　　　　　Compound C (1 gram, 1.37 mmol) was dissolved
in dry dimethylformamide (5.0 mL) and sulfur trioxide-
5　　pyridine complex (267.1 mg, 1.64 mmol) was added at
-30°C. The resulting solution was stirred at -30°C for
5 hours and then 15 hours at 0°C. Excess reagent was
destroyed by the addition of methanol (2 mL). The
The reaction mixture was converted into sodium salt by
10　passage through Dowex 50-X8 (Na+) resin in methanol.
Evaporation and co-evaporation with toluene left a
while solid which was purified by chromatography on
silica gel using dichloromethane-methanol-pyridine
(9:1:0.1) as eluant to provide the title compound as a
15　white solid. This material was converted into sodium
salt by passage through Dowex 50-X8 (Na+) resin in
methanol to give the title compound (850 mg, 74.6%).

Example 18 -- Synthesis of 8-Methoxycarbonyloctyl 3-O-
　　　　　(3-O-sulfo-β-D-galactopyranosyl)-2-acetamido-
20　　　　2-deoxy-β-D-glucopyranoside

　　　　　The product of Example 17 (800 mg, 0.96 mmol)
was dissolved in methanol (10 mL) containing 5%
palladium on carbon (800 mg) and was stirred under
hydrogen (1 atmosphere) for 5 hours at room
25　temperature. Catalyst was removed by filtration,
washed with methanol (500 mL) and the solvent was
evaporated to dryness. The residue was then purified
by chromatography on silica gel using dichloromethane-
methanol-water-pyridine (80:20:2:0.2) as eluant. The
30　title compound (488 mg, 77.5%) was obtained as a white
solid after BioGel P-2 (200-400 mesh) filtration and
conversion into its sodium salt. 1H.n.m.r. (D$_2$O)

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δ: 4.520-4.570 [m, 2h, incl. H-1(d, 4.550, $J_{1,2}$ 8.0Hz
and H1'(d, 4.542, $J_{1',2'}$ 7.7 Hz)], 4.277-4.343 [m, 2H,
incl. H-3'(dd, 4.310, $J_{2,3}$ 10.0Hz, $J_{3,4}$ 3.5Hz) and
H-4'(4.296)], 3.687(s, 3H, OCH_3), 2.388(t, 2H, J7.5Hz,
5   CH_2COO),2.025(s, 3H, NHAc), 1.570(m,4H) and 1.30(m,
8H).

The 2,3-disulfate of Example 18 was prepared
in a similar manner except that sulfation was conducted
with 6 equivalents of sulfur trioxide/pyridine complex
10   and the reaction was conducted at room temperature for
24 hours. The resulting product was a mixture of 2-,
3-sulfate and predominantly 2,3-disulfate. The mixture
was purified by chromatography in the manner described
and ion exchange of the resulting product provided for
15   the 2,3-disulfate of Lewis[c]-OR as the disodium salt.

The 2-sulfate of Lewis[c]-OR was prepared from
compound C by benzoylation under conditions described
above. The resulting product contained predominantly
the 3-benzoyl group on the galactose unit and a small
20   amount of the 2-benzoyl and 2,3-dibenzoyl derivatives.
The products were separated by chromatography on silica
gel to provide for both the 2-benzoyl and the 3-benzoyl
derivatives as pure products.

The 3-benzoyl derivative was sulfated in the
25   manner described above and then deprotected to provide
for the 2'-sulfo-Lewis[c]-OR which upon ion exchange as
described above provided for the sodium salt of this
product.

The 3'-sulfo-LacNAc derivative was prepared
30   from compound 42 (prepared in Example 6) wherein the
dibenzoyl groups are removed via Zemplen conditions

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(sodium methoxide/methanol) and then sulfated under the
conditions described above to provide for
3'-sulfo-Lewis^c-OR.

5   The following Examples 19-20 illustrate the
immunomodulating properties of the compounds of this
invention.

Example 19 - Inhibition of DTH Inflammatory Response
        DTH inflammatory responses were measured
using the mouse footpad swelling assay as described by
10   Smith and Ziola[14].   Briefly, groups of Balb/c mice were
immunized with 100 μg of the OVA antigen [Albumin,
chicken egg, Sigma, St. Louis, Missouri] containing
20μg of the DDA adjuvant (dimethyldioctadecylammonium
bromide) which has been shown to induce a strong
15   inflammatory DTH response. Seven days later, each
group of mice was footpad-challenged with 20 μg of OVA
antigen.   The resulting inflammatory footpad swelling
was measured with a Mitutoyo Engineering micrometer 24
hours after challenge.

20   To assess the effect of the analogues of
Lewis^c-OR and LacNAc-OR on the inflammatory DTH
response, groups of mice received 100 μg of the
following oligosaccharide glycosides 5 hours after
foot-pad challenge with the OVA antigen.

25   Compound A = 3'-Sulfo-Lewis^c-OR
                    [3'-sulfo-βGal(1-3)βGlcNAc-OR]

        Compound B = 2'-Sulfo-Lewis^c-OR
                    [2'-sulfo-βGal(1-3)βGlcNAc-OR]

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Compound C = Sialyl Lewis^X-OR
            [αNeu5Ac($2\rightarrow3$)βGal(1-4)-[α-L-Fuc(1-3)]-
            βGlcNAc-OR]

Compound D = Sialyl Lewis^A-OR (αNeu5Ac($2\rightarrow3$)βGal(1-3)-
            [α-L-Fuc(1-4)]-βGlcNAc-OR]

Compound E = Sialyl Lewis^c-OR
            [αNeu5Ac($2\rightarrow3$)βGal(1-3)-βGlcNAc-OR]

Percentage reduction in inflammation for this
example was calculated by the following equation:

$$100 - 100 \times \left[\frac{\text{Swelling of Treated Mice -bkg swelling}}{\text{Swelling of Untreated Mice - bkg swelling}}\right]$$

"Treated mice" are those mice which receive
one of the above compounds in addition to the antigen.
"Untreated Mice" are those mice which do not receive
any of the above compounds. Background (bkg) swelling
is that level of swelling observed in mice immunized
with PBS alone without antigen or compound and
challenged with antigen.

The results of this experiment are set forth
below:

Compound	% Reduction in Inflammation
A	~59%
B	~35%
C	~24%
D	~30%
E	~41%

In a separate study, 3'-sulfo-LacNAc was
shown to reduce inflammation by about 24% when
administered to OVA sensitized mice 5 hours after OVA
challenge in the manner described above.

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The above results demonstrate that the compounds of this invention are effective in treating mammalian cell mediated secondary immune responses arising from antigen challenge.

5   Example 21 --   Effect of Oligosaccharide Glycosides
                      on LPS Caused Lung Injury

LPS (lipopolysaccharide) caused lung injury is measured by weighing the lungs of sacrificed mice 24 hours after mice are given LPS intranasally. Briefly,
10   groups of 8-10 week old Balb/c mice were sensitized with 5 μg /mouse of LPS in 50 μl of PBS intranasally under light anesthesia.

The method of administering compound intranasally is described in Smith et al.[15], which is
15   incorporated by reference. Briefly, mice are anethesitized with Metofane (Pitman-Moore Ltd., Mississauga, Ontario, Canada) and a 50 μl drop of compound is placed on the nares of the mouse and is inhaled.

20   Five hours later, 100 μg/mouse of 3'-sulfo-Lewis[c]-OR in 200 μl of PBS is given to the mouse intravenously. After 24 hours, 48 hours or 72 hours, different groups of mice are sacrificed and the lungs removed and weighed. The weight of the lungs of mice
25   treated with 3-sulfo-Lewis[c]-OR are compared against control (i.e., mice treated with LPS but to which 3-sulfo-Lewis[c]-OR has not been administered). The percent reduction is measured by subtracting from 100 the following:

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The fraction derived by a numerator whose value is the weight of the treated lungs subtracted from the weight of normal lungs (lungs from mice not exposed to LPS, 3-sulfo-Lewis^c-OR), and whose

5   denominator whose value is the weight of the control lungs (mice that received only LPS) subtracted from the weight of normal lungs and multiplying the resulting fraction by 100.

The greater the percent reduction, the better

10   the compound is in allevating lung damage.

The results of this test are set forth below:

| Time	% Reduction in Inflammation
24 hours	~53%
48 hours	~27%
72 hours	~52%

15

The above data demonstrates that the compounds of this invention are effective in reducing

20   cell-mediated inflammatory responses due to injury.

WHAT IS CLAIMED IS:

1. A compound of Formula I or II:
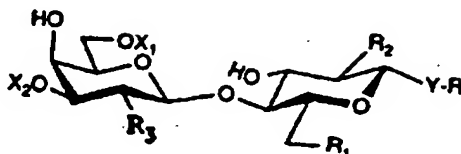
I
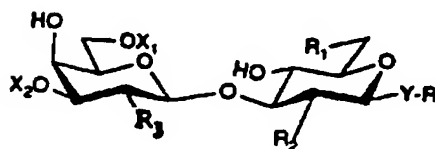
II

5   where R is selected from the group consisting of
hydrogen, a saccharide-OR_{19}, an oligosaccharide-OR_{19}
having from 2 to 7 oligosaccharide units, or an aglycon
having at least 1 carbon atom where R_{19} is hydrogen or
an aglycon of at least one carbon atom;

10   Y is selected from the group consisting of oxygen,
sulfur, and -NH-;

        R_1 is selected from the group consisting of
hydrogen, $-NH_2$, $-N_3$, $-NHSO_3H$, $-NR_5C(O)R_4$, $-N=C(R_5)_2$,
$-NHCH(R_5)_2$, $-NHR_6$, $-N(R_6)_2$, $-OH$, $-OR_6$, $-S(O)R_6$, $-S(O)_2R_6$

15   and sulfate,

        wherein R_4 is selected from the group consisting
of

                hydrogen,

                alkyl of from 1 to 4 carbon atoms;

20              $-OR_7$ wherein R_7 is alkyl of from 1 to 4 carbon
atoms, or alkyl of from 2 to 4 carbon atoms substituted
with a hydroxyl group, and

                $-NR_8R_9$ wherein R_8 and R_9 are independently
selected from the group consisting of hydrogen and

25   alkyl of from 1 to 4 carbon atoms,

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each R_5 is selected from the group consisting of hydrogen and alkyl of from 1 to 4 carbon atoms,

each R_6 is alkyl of from 1 to 4 carbon atoms,

R_2 is selected from the group consisting of hydrogen, $-N_3$, $-NH_2$, $-NHSO_3H$, $-NR_{11}C(O)R_{10}$, $-N=C(R_{11})_2$, $-NHCH(R_{11})_2$, $-NHR_{12}$, $-N(R_{12})_2$, $-OH$ and $-OR_{12}$,

wherein R_{10} is selected from the group consisting of

hydrogen,

alkyl of from 1 to 4 carbon atoms,

$-OR_{13}$ wherein R_{13} is alkyl of from 1 to 4 carbon atoms, or alkyl of from 2 to 4 carbon atoms substituted with a hydroxyl group, and

$-NR_{14}R_{15}$ wherein R_{14} and R_{15} are independently selected from the group consisting of hydrogen and alkyl of from 1 to 4 carbon atoms,

each R_{11} is selected from the group consisting of hydrogen and alkyl of from 1 to 4 carbon atoms;

each R_{12} is alkyl of from 1 to 4 carbon atoms,

R_3 is selected from the group consisting of hydrogen, fluoro, sulfate and hydroxy;

X_1 is selected from the group consisting of hydrogen, sialyl, sulfate, phosphate, and $-CHR_{18}COOH$ where R_{18} is selected from the group consisting of hydrogen, alkyl of from 1 to 7 carbon atoms and $-COOH$;

X_2 is selected from the group consisting of hydrogen, sulfate, phosphate, and $-CHR_{18}COOH$ where R_{18} is selected from the group consisting of hydrogen, alkyl of from 1 to 7 carbon atoms and $-COOH$; and

pharmaceutically acceptable salts thereof;

and with the proviso that either at least one of X_1 or X_2 is sulfate, phosphate or $-CHR_{18}COOH$ or R_3 is sulfate.

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2.   A compound of Claim 1 wherein said compound is of Formula I.

3.   A compound of Claim 1 wherein said compound is of Formula II.

5   4.   A compound of Claim 1 wherein R_1 is selected from the group consisting of hydroxyl, hydrogen or alkoxy of from 1 to 4 carbon atoms.

5.   A compound of Claim 1 wherein R_2 is selected from the group consisting of hydroxyl, alkoxy of from 1
10   to 4 carbon atoms, $-NH_2$, $-N_3$ and $-NHC(O)R_{10}$.

6.   A compound of Claim 1 wherein R_3 is -OH.

7.   A compound of Claim 1 wherein X and X_1 are hydrogen and X_2 is selected from the group consisting of sulfate, phosphate, and $-CHR_{18}COOH$.

15   8.   A compound of Claim 1 wherein X and X_2 are hydrogen and X_1 is selected from the group consisting of sulfate, phosphate, and $-CHR_{18}COOH$.

9.   A compound of Claim 2 wherein X_1 is hydrogen, X_2 is sulfate, R_1 is hydroxyl, R_2 is selected from the
20   group consisting of $-NH_2$ and $-NHC(O)CH_3$ and R_3 is hydroxyl.

10.   A compound of Claim 3 wherein X_1 is hydrogen, X_2 is sulfate, R_1 is hydroxyl, R_2 is selected from the group consisting of $-NH_2$ and $-NHC(O)CH_3$ and R_3 is
25   hydroxyl.

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11. A pharmaceutical composition suitable for administration to a mammal which comprises a pharmaceutically inert carrier and an effective amount of the compound of Claim 1 to modulate a cell-mediated

5   immune response in said mammal.

12. A method for modulating a cell-mediated immune response in a mammal which method comprises administering to said mammal an amount of a compound of Claim 1 effective in modulating said immune response.

10   13. A method for reducing sensitization of a mammal to an antigen which comprises administration of an effective amount to the mammal of a compound of Claim 1.

14. A method for reducing sensitization of a
15   mammal to an antigen which comprises administration of an effective amount to the mammal of a compound of Claim 2.

15. A method for reducing sensitization of a mammal to an antigen which comprises administration of
20   an effective amount to the mammal of a compound of Claim 3.

16. A method according to Claim 12 wherein said suppression of an immune response comprises suppression of a DTH response and induction of tolerance to an
25   antigen.

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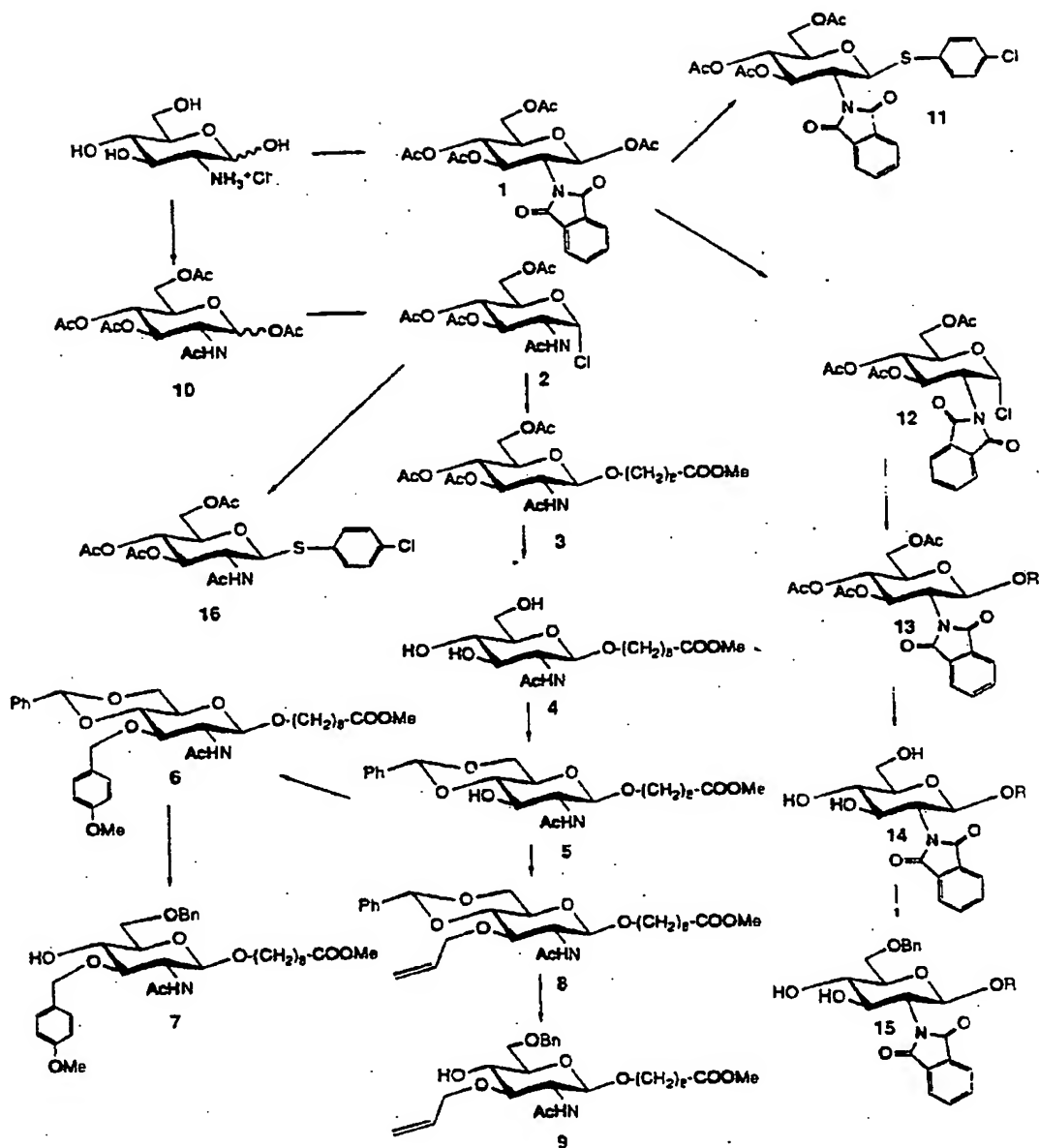
FIGURE 1

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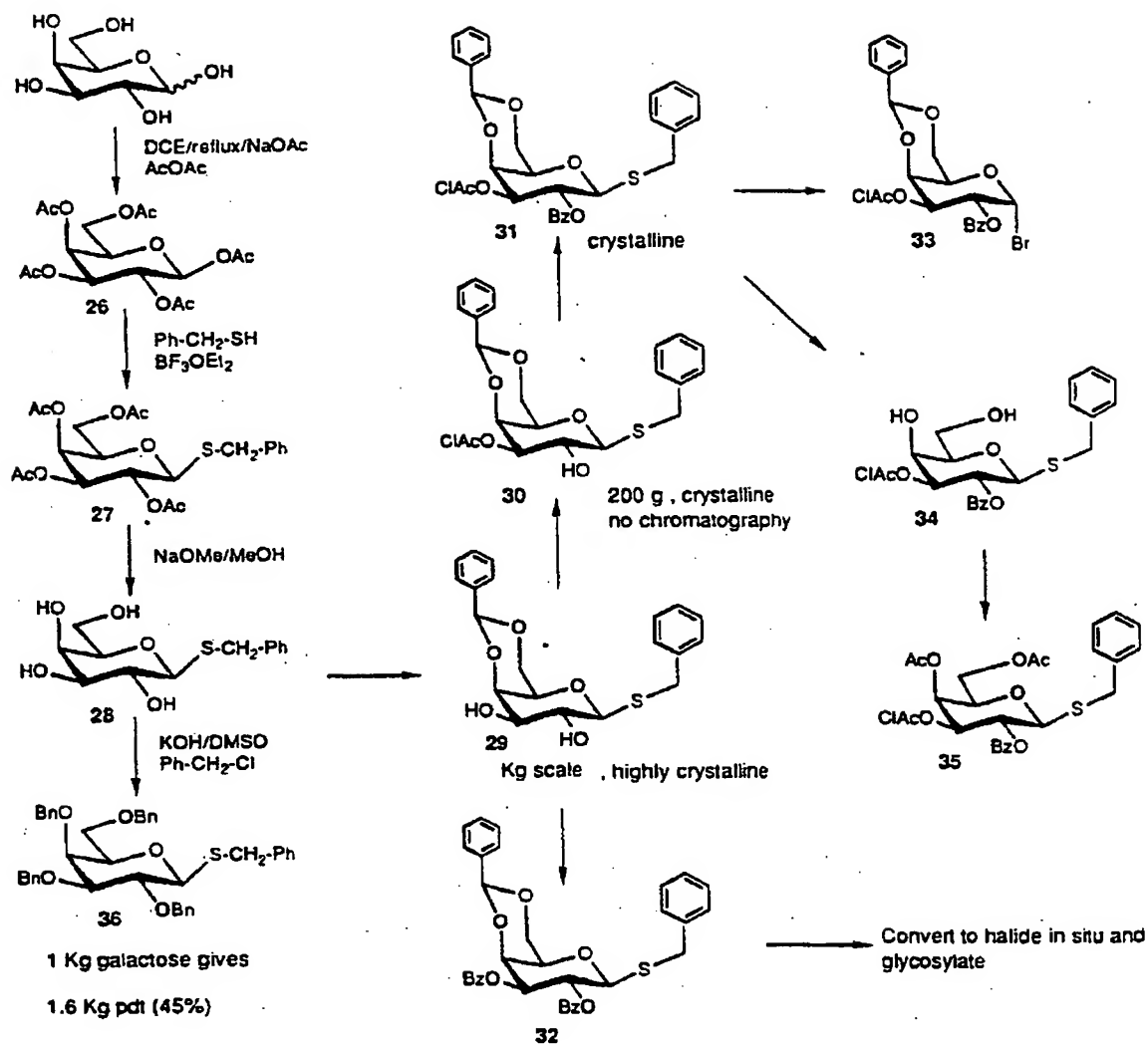
FIGURE 2

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3'-Sulfo-Lewis^c

-50°C 6-16 hours
DMF/SO₃-pyridine

104
+ 2' sulphate
+ 2', 3' disulphate

Na+ ion exchange
resin

105

+ 2' sulphate
+ 2', 3' disulphate
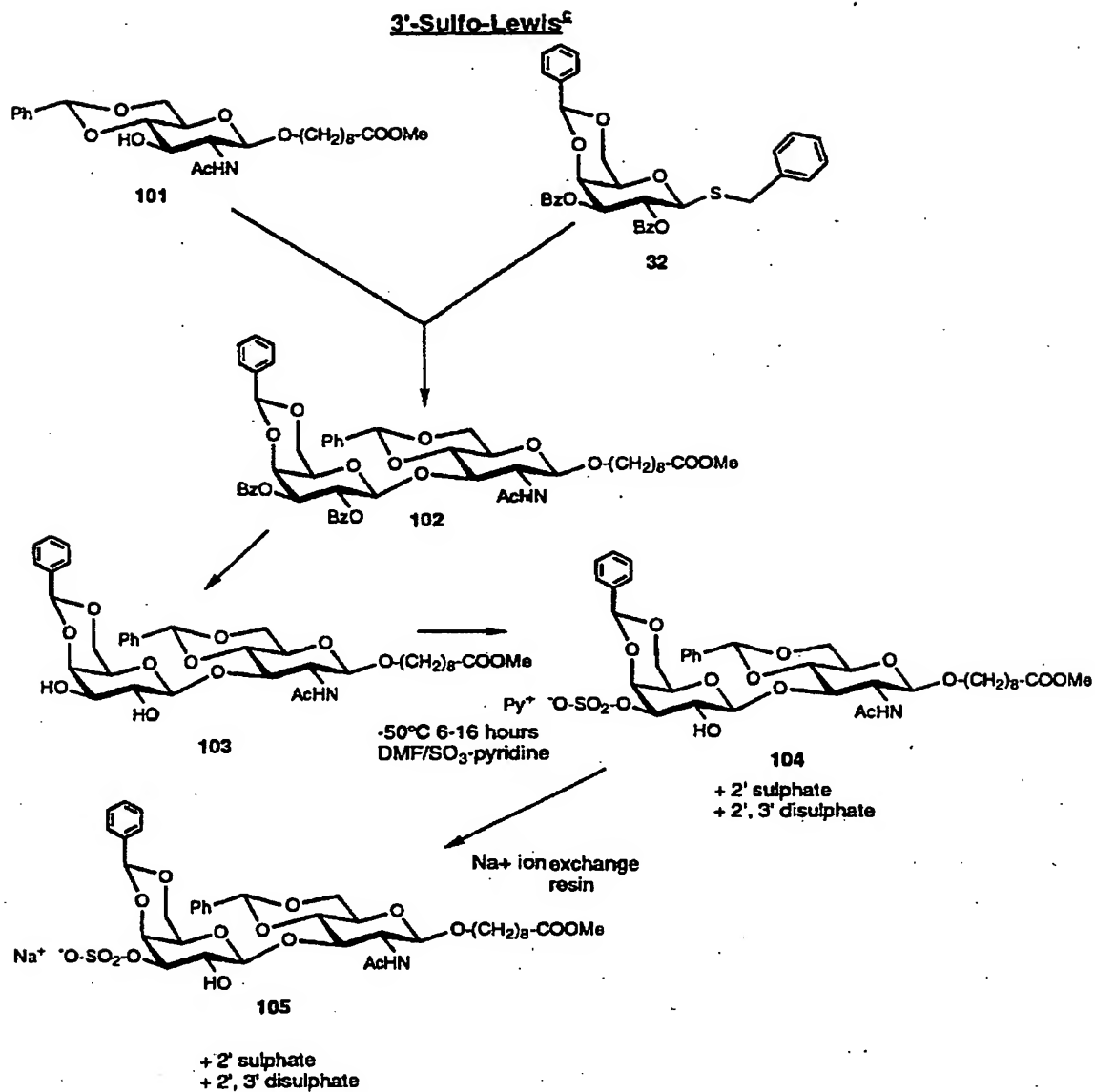
FIGURE 3A

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6'-sulfo Lewis c
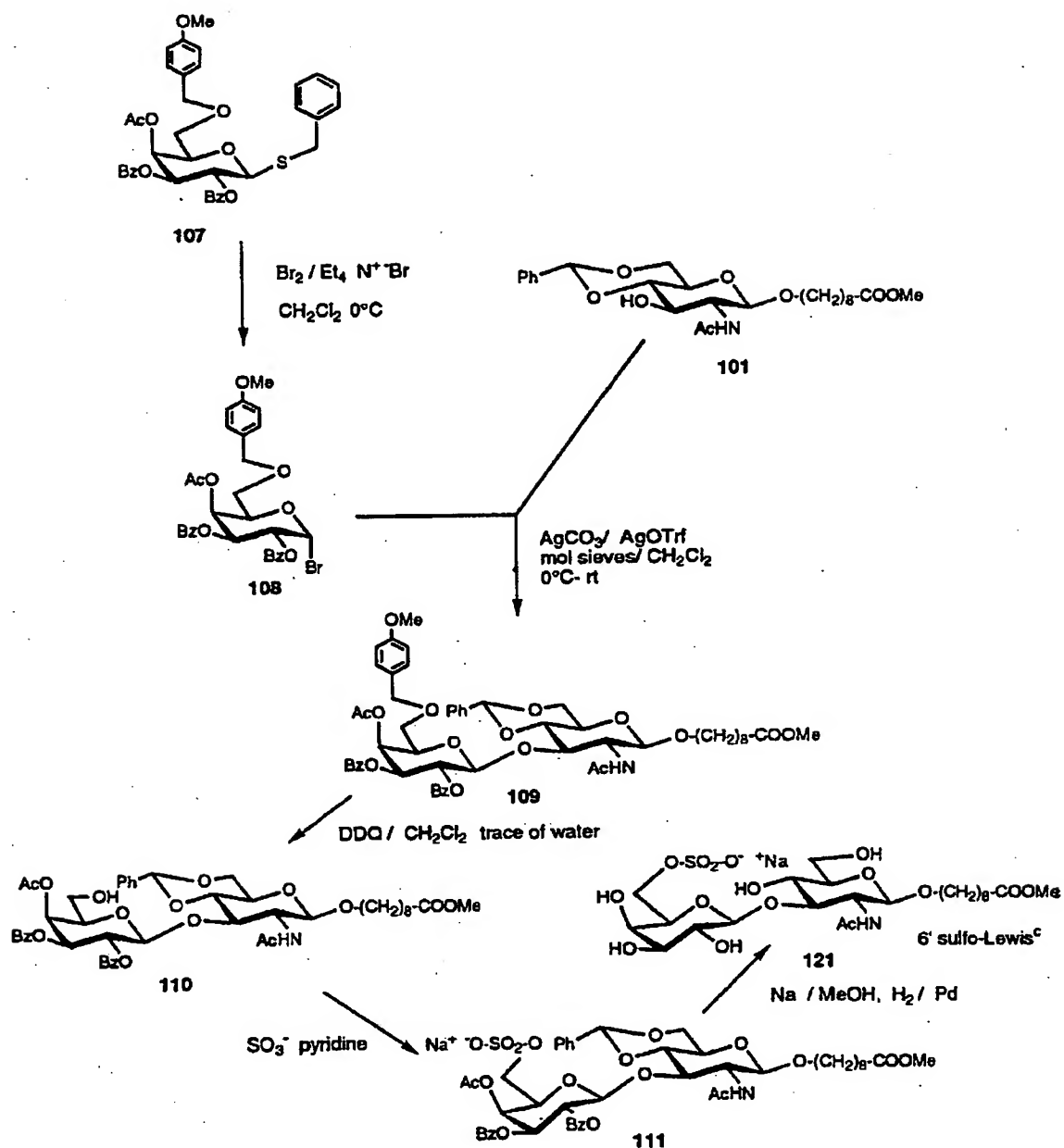
FIGURE 3B
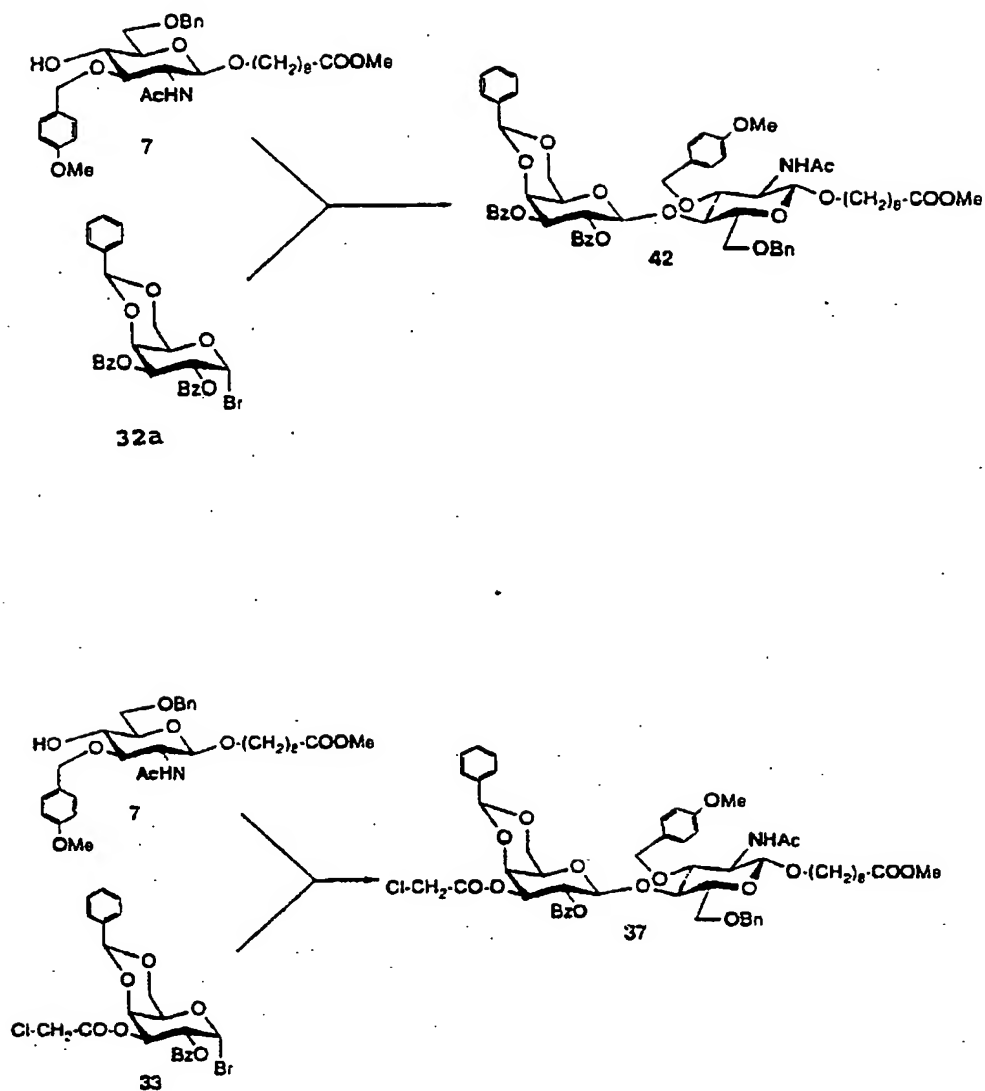
FIGURE 4

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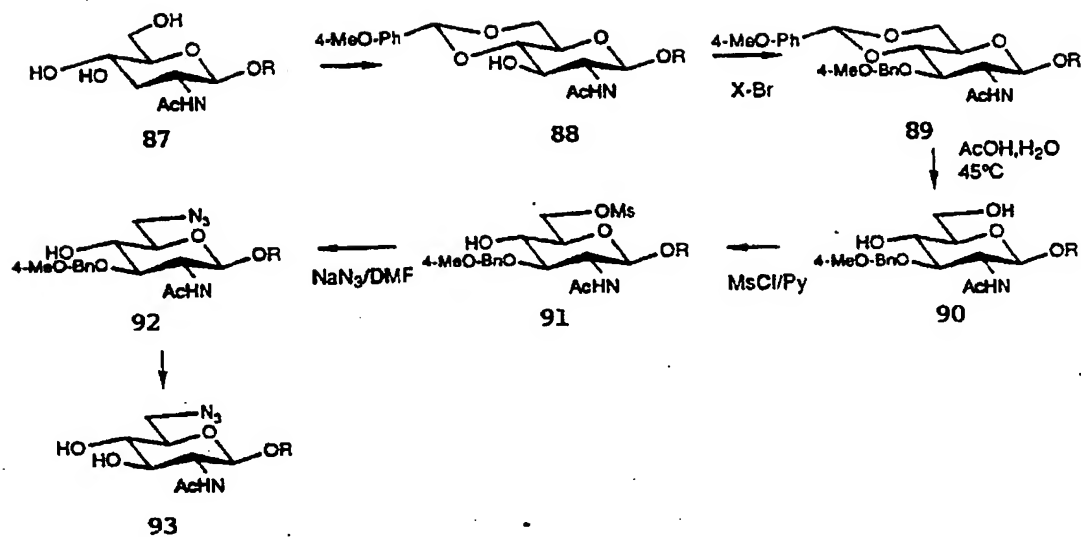
FIGURE 5
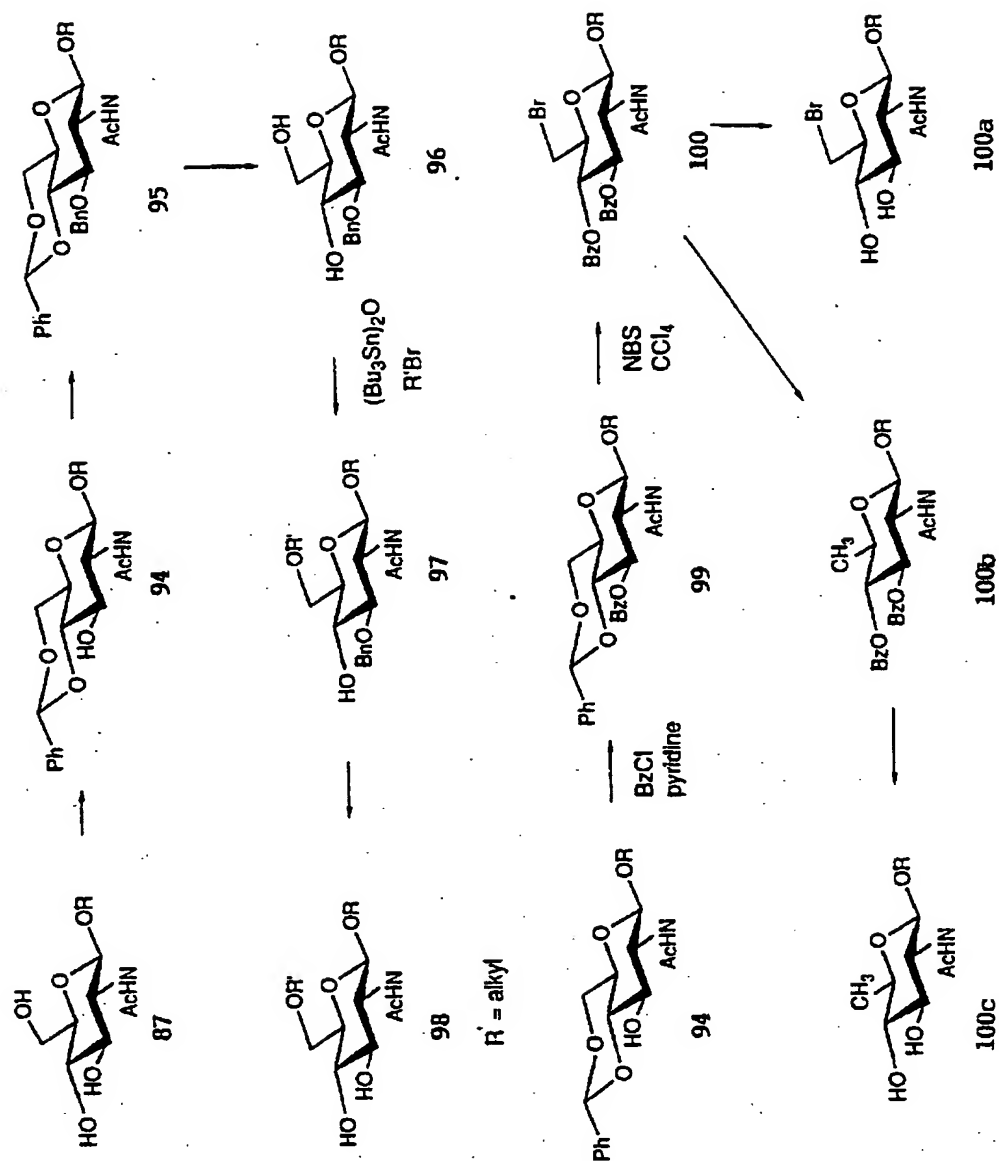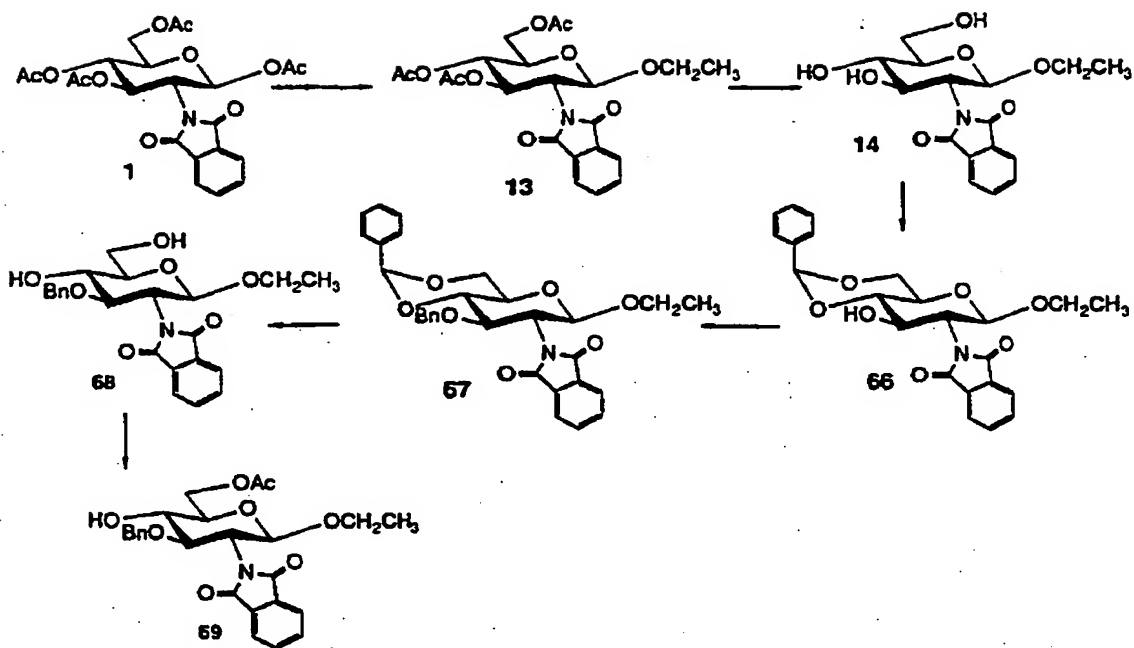
FIGURE 6

FIGURE 7

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INTERNATIONAL SEARCH REPORT

	International application No. PCT/US93/04995

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07H 15/06, 1/00, 17/00; A61K 31/70

US CL :514/54, 53, 49; 536/53, 55.1, 18.7, 18.2, 4.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/54, 53, 49; 536/53, 55.1, 18.7, 18.2; 4.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS: Lacnac compounds, Lewis compounds, immunosuppressive, pharmaceutical

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A 5,079,353 (Ratcliffe et al) 07 January 1992, see entire document	1-14
Y	US, A 5,079,235 (Purifoy et al) 07 January 1992, see entire document	1-14

☐ Further documents are listed in the continuation of Box C.   ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		
		"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 September 1993	14 SEP 1993

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	MICHAEL G. WITYSHYN
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